EXTRACRANIAL ANOMALIES OF THE COMMON CRANIOSYNOSTOSIS SYNDROMES

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Doctor of Medicine
University of Edinburgh
1997

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ACKNOWLEDGEMENTS

I am indebted to Dr Robert Evans of the Craniofacial Unit and Orthodontic Department at Great Ormond Street Hospital for his supervision and direction, his enthusiasm, and his constructive critical appraisal.

I am grateful to Mr Richard Hayward and Mr Barry Jones of the Craniofacial Unit at Great Ormond Street Hospital for enabling this project to be undertaken and for their forebearance in allowing modification of the project after reviewing the early results.

I thank Dr Christine Hall in the Department of Radiology at Great Ormond Street, for teaching me to study radiographs and confirming my interpretation of radiographs.

I thank Dr William Reardon of the Department of Genetics, Institute of Child Health, for making his data relating to the individual mutations available to me for the Crouzon and Pfeiffer syndrome cases, as well as his advice. I also thank Dr Andrew Wilkie and Dr Sarah Slaney of the Department of Molecular Biology at the John Radcliffe Infirmary, Oxford for providing the data relating to the mutations of the Apert syndrome cases.

Thanks are due to the staff in the Department of Medical Illustration at Great Ormond Street for the production of the high quality photographs. I also acknowledge the assistance given to me by the staff within the records department of the Radiology Department for help in locating radiographs.

I would like to thank Professor M. Poole of the University of Sydney, Mr T. Hide and Professor K. Moos of the University of Glasgow who first introduced me to Craniofacial surgery in Oxford and Glasgow.

I also acknowledge Mr W. Scobie and Mr J. Orr in the Department of Paediatric Surgery at the Royal Hospital for Sick Children in Edinburgh, and Mr J. M. T. Griffiths at the Eastern General Hospital, Edinburgh who encouraged me to undertake clinical research as part of contemporary surgical practice.

Finally, I wish to thank my wife both for her assistance with proof reading and also for her continuous support with this venture.

DECLARATION

"I declare that the contents of this thesis, submitted to the University of Edinburgh for the degree of Doctor of Medicine, were composed entirely by myself. This thesis is based on my own observations, the data collected and the results analysed and interpreted by myself."

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This thesis is dedicated to Mandy, Hazel, Emily, and Ross who have unselfishly made many sacrifices to allow the completion of this work.

ABSTRACT

This thesis describes the clinical and radiological investigations into the anomalies which occur extracranially in the four most common craniosynostosis syndromes eponymously named Crouzon, Pfeiffer, Apert and Saethre-Chotzen. The anomalies include fusions of various components of the skeleton as well as congenital skeletal malformations. However, a range of variable anomalies existed for each syndrome and overlap of clinical features between the syndromes was commonly observed.

The cervical spine radiographs demonstrated anomalies at a higher incidence than previously published reports based on smaller samples for Pfeiffer and Saethre-Chotzen syndrome. However, the incidence of fusions in Crouzon syndrome was smaller. These results were partly due to the inclusion of atypical phenotypes whose diagnosis was assisted by D.N.A. analysis.

The hands and feet demonstrated a wider range of anomalies, occurring at higher incidence, than previous reports for Crouzon, Pfeiffer and Saethre-Chotzen syndromes, and include new findings. Skeletal anomalies are present at other sites including the elbows, the shoulders, the pelvis, and the knees in Crouzon, Pfeiffer and Apert syndromes but not in Saethre-Chotzen syndrome.

This study has identified sites of fixed and progressive extracranial anomalies present in each syndrome. The anomalies identified have been compared for the four syndromes studied and a comparison has been made where possible between the different genotypes within each syndrome, where these are known.

This work highlighting the existence of a greater range of extracranial anomalies in these syndromes, will assist clinicians in the diagnosis and management of affected children. These findings are also of interest to Developmental Biologists who are investigating the complex biological processes in human development.

CHAPTER ONE

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GENERAL INTRODUCTION

Craniosynostosis is the result of premature fusion of one or more sutures of the skull. This can occur either in apparently normal sutures, or because the sutures themselves may develop in an abnormal manner (Cohen, 1993b). It is a relatively common developmental anomaly and has been estimated to occur with an incidence of 1 in 2500 children (Gorlin *et al.,* 1990). Craniosynostosis may be the end result of several different disease mechanisms, which can be influenced by genetic and environmental factors (Cohen, 1993b). It may occur in conjunction with other malformations, and characteristic patterns of presentation have been recognised as distinct syndromes. Currently over 100 such syndromes are recognised (Winter and Baraitser, 1995). Many attempts have been made to classify craniosynostosis, including the division into simple and complex forms on the basis of whether or not there are extracranial findings (Cohen, 1986).

Craniosynostosis syndromes are inherited in a Mendelian manner. Although examples of all types of inheritance patterns are found, the more common Craniosynostosis syndromes (which includes those in this study) are autosomal dominant. The most common craniosynostosis syndromes are the eponymously named syndromes of Crouzon, Apert, Pfeiffer and Saethre-Chotzen. In addition to the craniosynostosis, anomalies of the extracranial skeleton affecting the cervical spine and hands and feet (except in Crouzon syndrome), are also present in these syndromes. However, with a few exceptions (see below), much of the information on the extracranial anomalies has

arisen from case reports or small series studies. Clinically, the most obvious of these anomalies is syndactyly affecting the hands. The association of hand syndactyly and craniosynostosis was recognised in the early studies of Apert syndrome and led to the use of the term acrocephalosyndactyly (Park and Powers, 1920). This broadened to the acrocephalosyndactyly syndromes when it became obvious that there were several different syndromes with anomalies of the hands in association with craniosynostosis (Blank, 1960; Temtamy, 1966). These include (in descending order of severity of hand manifestations) Apert, Pfeiffer and Saethre-Chotzen syndromes. This use of the term acrocephalosyndactyly to classify conditions with craniosynostosis and limb anomalies has changed with the clarification of the range of anomalies associated with each of the different syndromes. Apert syndrome is still sometimes referred to as acrocephalosyndactyly type 1, Saethre-Chotzen syndrome as type III and Pfeiffer syndrome as type V (McKuisick, 1992), but the acrocephalosyndactyly types II and IV (also eponymously named Vogt's, and Mohr's syndromes) are now recognised as variations of established craniosynostosis syndromes (McKuisick, 1992). The classification was further complicated when Waardenburg syndrome, which was originally known as acrocephalosyndactyly type V, was also deleted. Pfeiffer syndrome which had originally been called type VI became type V (McKuisick, 1992; Reardon and Winter, 1995). Crouzon syndrome has been reported not to have associated hand and feet abnormalities and so has not been accepted as an acrocephalosyndactyly syndrome (Cohen 1986; Reardon and Winter, 1995).

These complex craniosynostosis syndromes all have a range of phenotypic presentation, with some overlap between the syndromes. This makes the diagnosis, particularly of atypical phenotypes difficult on clinical examination. The mutations associated with Apert, Crouzon and Pfeiffer syndromes have been identified and are known to involve mutations of the fibroblastic growth factor receptor (FGFR) genes (Reardon *et al.*,1994; Muenke *et al.*, 1994; Wilkie *et al.*, 1995b; Rutland *et al.*, 1995). The individual results of D.N.A. analysis can be used clinically as an aid in diagnosis, particularly of atypical phenotypes. One early result of the introduction of D.N.A. analysis in the United Kingdom is that in two of the Supraregional Craniofacial Units, some of the patients with atypical phenotypes have had their original diagnosis reviewed (Anderson *et al.,* 1996a). This has important consequences both for the individuals concerned and also raises the possibility that previous studies of Crouzon, Pfeiffer and Saethre-Chotzen syndromes, may have included atypical examples of other syndromes (Anderson *et al.*, 1996a). This problem does not apply to Apert syndrome as the diagnosis is usually readily apparent. Diagnosis of a particular syndrome cannot however always be directly related to genotype alone. A number of genotypes have been identified (currently three) which can produce either Crouzon or a Pfeiffer phenotype (Rutland *et al.,* 1995). Also, there are two genotypes which can produce either a Crouzon or a Jackson-Weiss phenotype (Jabs *et al.,* 1994). (Jackson-Weiss syndrome is a much rarer craniosynostosis syndrome). The clinical features of the typical phenotype found in each of the four common craniosynostosis syndromes will be described.

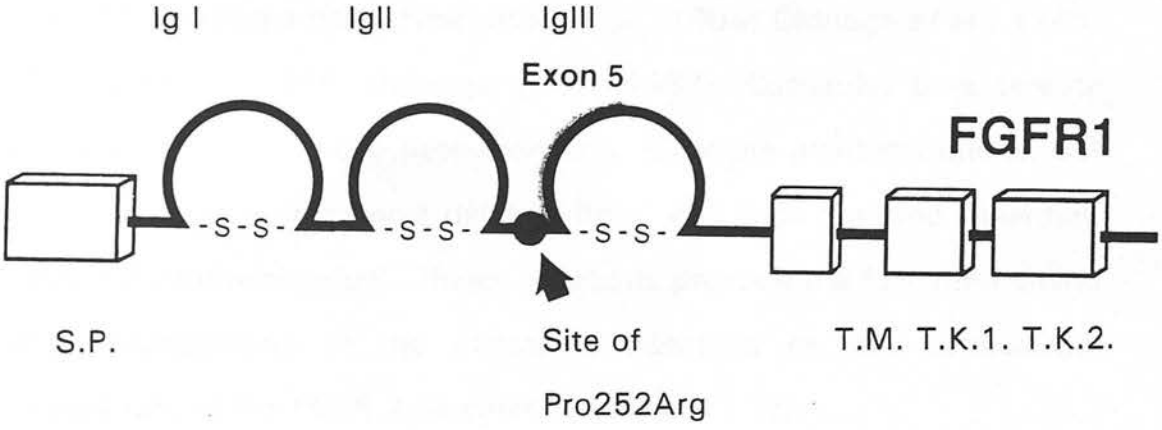
The syndrome of "Craniofacial dysostosis" was described by Crouzon (1912) and is still used by some authors. However, the condition had been previously described by several authors in the nineteenth century (Kreiborg, 1981). This condition is the most common of the craniosynostosis syndromes, with a reported incidence of 1 : 25,000 in the general population (Cohen, 1986). Many series of cases include examples where the condition has been familial (44% - 67% of cases), the remainder resulting from new mutations (Atkinson, 1937; Kreiborg, 1981).

The clinical features of Crouzon syndrome have been previously described by many authors, but current knowledge owes much to the findings of the study by Kreiborg (1981). Crouzon syndrome shows variable phenotypic expression but is characterised by the anomalies of the craniofacial skeleton: craniosynostosis, maxillary hypoplasia, shallow orbits leading to occular proptosis (Gorlin *et al.,* 1990). Extracranial anomalies have been reported in Crouzon syndrome. Anomalies of the cervical spine (cervical fusions) are well recognised in this syndrome (Kreiborg, 1981). However, uncertainties exist regarding both the existence and extent of anomalies of the limbs which continue to be reported as normal (Reardon and Winter, 1995; Al-Quattan and Al-Husain, 1996). These reports contradict an earlier study which identified anomalies of the extracranial skeleton, most commonly affecting the elbows and the cervical spine (Proudman *et al.,* 1994).

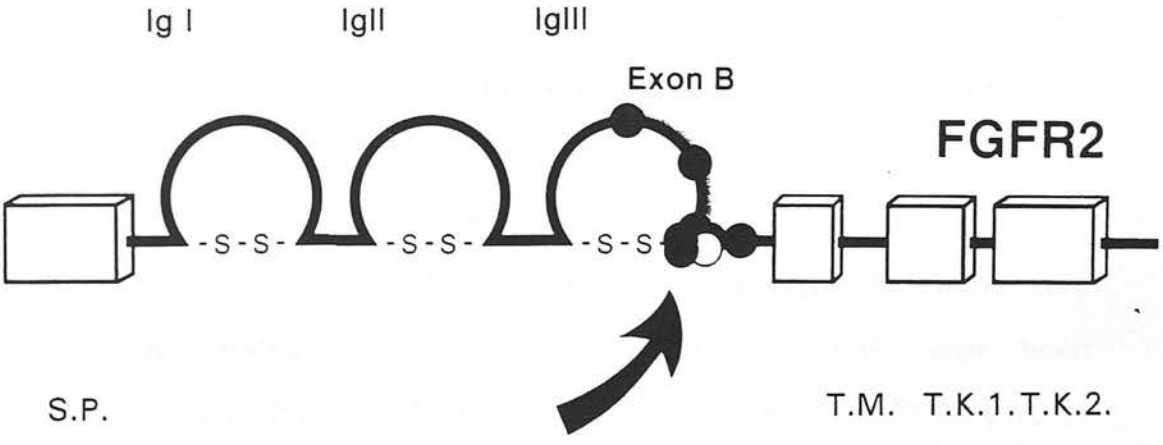
Crouzon syndrome is an autosomal dominant condition. Most of the mutations which have been identified affect the type 2 FGFR's (FGFR 2), see Figure 1.1, although a few cases, who also have associated acanthosis nigricans, result from mutations of the FGFR 3 receptor

FIGURE 1.1 STRUCTURE OF THE FIBROBLASTIC GROWTH FACTOR RECEPTORS (FGFR'S)

FGFR 1



FGFR 2



Key:

S.P. = Signal peptide, T.M. = Transmembrane domain

T.K. 1. = Tyrosine kinase domain 1, T.K. 2. = Tyrosine kinase domain 2.

(Meyers *et al.,* 1995; Wilkes *et al.,* 1996). The responsible gene for FGFR 2 is located on the long arm of chromosome 10 (Reardon *et al.*, 1994), while the gene for FGFR 3 is on the short arm of chromosome 4 (Meyers *et al.,* 1995). However, since the first report many more mutations of FGFR 2 have been identified which may produce a Crouzon syndrome phenotype (Jabs *et al.,* 1994; Oldridge *et al.,* 1995; Meyers *et al.,* 1996; Oldridge *et al.,* 1997). Currently, over twenty different mutations have been identified. Most are point mutations, but two examples of intragenic deletion have also been reported (Reardon, personal communication). These mutations produce the following amino acid substitutions at the numbered positions of the extracellular component of the FGFR 2 receptor (see Figure 1.1):

Tyr105Cys, Ser252Leu, Ser267Pro, Cys278Phe, DelHis-ile-Gln287-289, Gln289Pro, Trp290Gly, Trp290Arg, Tyr328Cys, Ala337Pro, Gly338Arg, Gly338Glu, Tyr340His, Thr341Pro, Cys342Ser, Cys342Arg, Cys342Phe, Cys342Tyr, Cys342Trp, Ala344Gly, activation splice site 344(Ala344Ala), Ser347Cys, Ser354Cys. (Reardon *et al.,* 1994; Heutnik *et al.,* 1995; Oldridge *et al.,* 1997; Reardon, personal communication).

The Cys278Phe, Cys342Ser, and Cys342Arg mutations are particularly interesting because the same mutations have been demonstrated in Pfeiffer phenotypes (Rutland *et al.,* 1995; Meyers *et al.,* 1996).

The Ala344Gly mutation in the FGFR 2 gene is also notable since this mutation was first described in another craniosynostosis syndrome, (the rarer Jackson-Weiss syndrome), (Jabs *et al.,* 1994; Gorry *et al.,* 1995). This syndrome has particularly variable clinical features so making

diagnosis difficult. Recently, the Gln289Pro mutation in the FGFR 2 gene has also recently been identified in a Jackson-Weiss phenotype (Meyers *et al.,* 1996). This has led to the suggestion that instead of being a distinct clinical entity, Jackson-Weiss syndrome is related to Crouzon syndrome (Meyers *et al.,* 1996).

The FGFR 3 mutation which has been identified in unrelated Crouzon phenotypes affects the amino acids in the transmembrane part of the receptor producing an Ala391Glu substitution (Meyers *et al.,* 1995; Wilkes *et al.,* 1996).

Pfeiffer syndrome has only been recognised as a distinct entity relatively recently (Pfeiffer, 1964). This is in part due to the range of severity of clinical findings, which can be so marked in this condition that it has been suggested that three clinical sub-types can be identified (Cohen, 1993a). Prior to the discovery of this syndrome severely affected phenotypes with syndactyly had often been labelled "atypical" or "mild" Apert syndrome or given the general term acrocephalosyndactyly (Blank, 1960). Conversely, atypical phenotypes with mild anomalies have been mis-diagnosed as Crouzon syndrome (Anderson *et al.,* 1996a). The incidence of Pfeiffer syndrome is not recorded, but undoubtedly it is less common than Crouzon syndrome.

Pfeiffer syndrome is characterised clinically by the combination of craniosynostosis producing a turribrachycephalic skull; maxillary hypoplasia leading to occular proptosis; hypertelorism; and down slanting palpebral fissures. These are all associated with hand and feet anomalies (Gorlin *et al.* 1990). Classically, the limb anomalies consist of broad thumbs and toes with variable syndactyly (Gorlin *et al.* 1990). The

incidence and severity of anomalies of the extracranial skeleton at other sites have been difficult to establish because of the rarity of this condition. Extracranial anomalies have on occasion been described in small series (Saldino *et al.,* 1972; Gorlin *et al.,* 1990), and an increased incidence of fusions of the cervical spine has been reported (Hemmer *et al.,* 1987; Moore *et al.,* 1995).

Pfeiffer syndrome is an autosomal dominant condition and both familial and spontaneous new cases have been reported. The same phenotypic appearance can result from mutations affecting two different types of FGFR, either the type 2 or the type 1 FGFR's (Muenke *et al.,* 1994; Rutland *et al.,* 1995; Schell *et al.,* 1995). Only one mutation of the FGFR 1 gene has been identified which will produce a Pfeiffer syndrome phenotype. This has been identified as a Pro252Arg change. However, since FGFR 2 mutations were first reported as producing a Pfeiffer phenotype there have been many further mutations identified (Meyers *et al.,* 1996; Oldridge *et al.,* 1997) and currently over ten different FGFR 2 mutations which produce a Pfeiffer phenotype have been described (Reardon, personal communication). The following missense mutations of FGFR 2 have been observed: Ser252Phe and Pro253Ser (double amino acid substitution), Cys278Phe, Asp321Ala, Cys342Ser, Cys342Arg, Ala344Pro, Val359Phe (Rutland *et al.,* 1995; Meyers *et al.,* 1996; Oldridge *et al.,* 1997; Reardon, personal communication). In addition to these at least three splice site mutations have been identified (Reardon, personal communication). Most of the Pfeiffer syndrome genotypes currently identified have one of the FGFR 2 mutations.

The Cys278Phe, Cys342Ser, and Cys342Arg FGFR 2 gene mutations are the same mutations referred to earlier involved in the production of Crouzon phenotypes (Rutland *et al.,* 1995; Meyers *et al.,* 1996).

The curious finding of mutations of different genes producing the same syndrome phenotype (locus heterogenicity) is further complicated because the different FGFR genes are found on different chromosomes. FGFR 1 gene is located on the short arm of chromosome eight (Muenke *et al.,* 1994) while the FGFR 2 gene is found on the long arm of chromosome 10 (Reardon *et al.,* 1994).

Eugene Apert first called the condition now named eponymously after him, acrocephalosyndactyly (Apert, 1906). This condition like Crouzon syndrome, had been previously described (Wheaton, 1894). The incidence has been reported as occurring between 1:100,000 (Tunte and Lenz, 1967), and 1: 160,000 live births (Blank, 1960). Despite the rarity of the condition, the clinical features of Apert syndrome have been studied by more authors than any of the other three most common craniosynostosis syndromes. The head is broad with the metopic and sagittal sutures widely patent during infancy resulting in turribrachycephaly (Gorlin *et al.,* 1990). Maxillary hypoplasia resulting in shallow orbits and proptosis; hypertelorism, and downslanting palpebral fissures are common findings, along with more widespread extracranial anomalies. These include the universal finding of syndactyly of the hands and feet, but anomalies of the elbows and shoulders and the viscera have also been reported (Gorlin *et al.,* 1990). Affected individuals have clinically obvious anomalies of the skeleton (head, hands and feet), and the central nervous system (often resulting in

impaired mental function) and require assistance from a wide range of medical and surgical specialists.

Apert syndrome is an autosomal dominant condition with most cases occurring as spontaneous mutations, although a few examples of transmission are recorded (Gorlin *et al.,* 1990). The paternal age has long been thought to be important (Blank, 1960) and recently confirmation that the mutation originates in the father's sperm has been reported (Moloney *et al.,* 1996). The mutation also affects the FGFR 2 but in contrast to Crouzon and Pfeiffer syndrome just a single further genotype has been reported since the first two mutations were originally identified (Wilkie *et al.,* 1995b; Oldridge *et al.,* 1997). With the exception of a single case, all the Apert syndrome cases where the mutation has been identified, belong to one of the two originally described mutations.

These two mutations of the FGFR 2 involve adjacent amino acids and are either Ser252Trp or Pro253Arg. These are found in the linker region between the second and third immunoglobulin domains (Wilkie *et al.,* 1995b), see Figure 1.1. The third recently described mutation Ser252Phe was identified in a single case (Oldridge *et al.,* 1997), but requires a double mutation, which explains its rarity. Interestingly, the possibility of this mutation had been predicted at the time the other two were described (Wilkie *et al.,* 1995b).

Saethre-Chotzen syndrome was first described independently by two psychiatrists (Saethre, 1931; Chotzen, 1932). Although further cases were subsequently described, due to the variability of expression, it was

not until the 1960's that it was appreciated that these were all forms of the same condition (Temtamy and McKusick, 1969).

Saethre-Chotzen syndrome has the following clinical features in its classical presentation: craniosynostosis, which can be variable, but which most commonly affects the coronal sutures producing brachycephaly (or plagiocephaly if asymmetrical involvement), along with a low set hair line, ptosis of the eyelids, strabismus and partial syndactyly of the hands (Gorlin *et al.,* 1990). However, the presentation can be extremely variable and mildly affected adults have sometimes been diagnosed retrospectively only when more severely affected children and grandchildren have required treatment.

The syndrome follows an autosomal dominant mode of transmission with complete penetrance but wide expressivity, and most cases are familial. The mutation responsible for this condition has not yet been identified, but there is evidence that it is on the short arm of chromosome 7 (Reardon *et al.*, 1993; Reid *et al.,* 1993), with a familial translocation reported in the 7p21/22 region of unrelated Saethre-Chotzen phenotypes. This mutation does not involve the fibroblastic growth factor receptors (unlike Crouzon, Pfeiffer and Apert syndromes), so that any anomalies which occur are the result of a different process. This makes comparison of the sites and severity of anomalies in Saethre-Chotzen syndrome with those in the three other syndromes of particular interest. In the absence of an identified mutation the clinical presentation is currently still the method of establishing the diagnosis, and given the especially wide phenotypic variation of the condition, this can be difficult.

As discussed earlier, the phenotype of Crouzon, Pfeiffer, Jackson-Weiss and Apert syndromes can all result from mutations of the FGFR 2 gene. The anomalies present in these syndromes stems from a disturbance of normal FGFR function (Wilkie *et al.,* 1995a). The main function of FGFR's in unaffected individuals is to mediate the biological action of fibroblastic growth factors (FGF's), a family of nine cytokines (Mason, 1994). The FGF's are mitogens and are important in cell proliferation and differentiation during embryological development (Wilkie *et al.,* 1995a; Reardon and Winter, 1995). They have been shown to be particulaly important in the initial induction and sustained growth of the limb buds during embryogenesis (Niswander *et al.,* 1993).

The family of FGFR's are structurally diverse molecules which are functionally different (Johnson and Williams, 1993). These receptors are single membrane spanning tyrosine kinases. Four types of receptor are recognised in humans, types 1, 2, 3 and 4. These four receptors share a 56 - 71% amino acid identity (Cohen, 1995), but molecules with similar biochemical composition are found in many other eukaryotic species (Reardon and Winter, 1995). Although some binding properties are held in common for the four human FGFR's, there are functional differences and their distribution is different (Reardon and Winter, 1995; Wilkie *et al.,* 1995a; Cohen, 1995).

The FGFR molecule is complex containing an extracellular ligand binding region, composed of three immunoglobulin like domains, with a signal peptide, a transmembrane domain, and two intracellular tyrosine kinase domains. (Reardon and Winter, 1995), see Figure 1.1. The extracellular immunoglobulin-like domains (IgI, IgII and IgIII,

respectively), have cysteine residues present which are particularly important in determining the three dimensional structure of the receptor. Thus mutations affecting cysteine residues are particularly likely to change FGFR receptor configuration and function. This is highlighted by cysteine residue 342 in the IgIII domain of FGFR 2, which has been described as a "hot spot" for mutations because of the number of Pfeiffer or Crouzon phenotypes who demonstrate a mutation at this site (Meyers *et al.,* 1996). The IgIII site in FGFR 2 is also known to be an important site for ligand binding (Hou *et al.,* 1992; Cheon *et al.,* 1994).

Both FGFR 1 and FGFR 2 can have alternative splicing arrangements within the gene structure, so they can exist in different isoforms (Johnson and Williams, 1993). In FGFR 2 this results in alternative exons in the second half of the third immunoglobulin domain (IgIIIc). This can be either a B exon or a K exon and there are differences in function between the two (Reardon and Winter, 1995).

Those mutations affecting sites within the IgIII of FGFR 2 were the earliest identified sites to produce either Pfeiffer or Crouzon syndrome phenotypes, especially IgIIIc (B Exon in Figure 1.1), and this remains the commonest site for Crouzon and Pfeiffer mutations. The two common mutations producing an Apert phenotype occur in the linker region between the IgII domain and the IgIII domain (Wilkie *et al.,* 1995b), where an increasing number of mutations producing Crouzon and Pfeiffer phenotypes are now also been reported (Oldridge *et al.,* 1997). Recently, a mutation in the Ig I domain has been found to produce a Crouzon phenotype (Pulleyn *et al.,* 1996) and mutation of the FGFR 3 may also produce a Crouzon phenotype (Meyers *et al.,*

1995). Clearly, the relationship between the site of mutation and the resulting phenotype is a complex one.

The FGFR's are normally expressed as various isoforms and are part of a signalling pathway that regulates cell proliferation, differentiation, migration and survival in embryonic development, malignancy, wound healing and angiogenesis (Heutink *et al.,* 1995). The receptor signalling pathway is activated by ligand binding and results in dimerization and phosphorylation of the intracellular tyrosine residues of the receptor. The activated FGFR's may initiate several pathways (Park *et al.,* 1995a). The major pathway (which is the only one known to occur *in vivo*) involves the activation of a GTP-binding protein and the recruitment of protein kinases and phospholipase C. This results in an increase in intracellular calcium concentration (Mason, 1994; Park *et al.,* 1995a).

The description of FGFR expression (and splice variants) in development is incomplete but it has been suggested that each receptor isoform exhibits a characteristic pattern of distribution in both embryonic and adult life, and many tissues and cells express multiple FGFR genes and splice variants (McDonald and Heath, 1994). Currently, it is known that during development FGFR 1 transcripts are expressed predominantly in the brain and mesenchymal tissues. In adults they are found in brain, bone, kidney, skin, lung, heart and muscle but not in liver (Johnson and Williams, 1993). However, during development FGFR 2 transcripts are expressed preferentially in brain, frontal bone maxilla, mandible, middle ear ossicles, developing limb buds (especially in the interdigital webs) and epithelium, while in the adult they are found in brain, kidney, skin, lung and liver, but not in

heart, spleen or muscle (Johnson and Willams, 1993; Reardon and Winter, 1995). There is differential expression of the two forms of FGFR 2 with the B exon form expressed during osteogenesis, while the K exon form is concentrated in the epithelia (Orr-Uretreger *et al.,* 1993). Also while the K exon has a high affinity for FGF 7 (keratinocyte growth factor), the B exon has little or no affinity for FGF 7 (Reardon and Winter, 1995).

In summary, there can be little doubt that FGFR biology is complex. The exact processes may be yet further complicated since it has been suggested that FGFR 4 may also have a role in the production of anomalies associated with craniosynostosis syndromes (Johnson *et al.,* 1994; Roberts and Tabin, 1994).

The discovery that the mutational basis of Crouzon, Pfeiffer and Apert syndromes affects FGFR's, and that these are known to be widely distributed, raises the possibility that the abnormal FGFR's in these syndromes could be expressed at many sites and produce anomalies there. Currently, anomalies are known to exist in the cervical spine, hands and feet. As FGFR 2 is important in osteogenesis, then any subtle anomalies are likely to affect the skeleton and may require radiological examination to identify them. Any such anomalies will have to be carefully examined to determine if they have arisen as a consequence of the underlying mutation, and if so, constitute part of the syndrome.

The new genetic findings in these craniosynostosis syndromes resulting from the use of D.N.A. analysis, has led to the identification of populations less likely to be contaminated with other syndromes. This provides an opportunity to re-evaluate the extracranial features

associated with each syndrome. For this to be possible, given that the range of phenotypic appearances is variable, a relatively large population of children with these rare syndromes is required, to establish the incidence and the range of anomalies associated with each syndrome. Previous studies of these syndromes have often used relatively small numbers of cases, although there have been some notable exceptions. These include the Crouzon syndrome study by Kreiborg (1981); Saethre-Chotzen syndrome studies by Pantke *et al.,* (1975) and Shalin *et al.,* (1993), and Apert syndrome, which has been the most closely studied syndrome (Park and Powers, 1920; Blank, 1960; Upton and Zucker, 1991; Cohen and Kreiborg, 1993c; Slaney, 1996).

The purpose of this study was to establish the range and incidence of the extracranial anomalies found in patients with Crouzon, Pfeiffer, Apert and Saethre-Chotzen syndromes, attending the Craniofacial Centre at Great Ormond Street Hospital. This was done using a combination of clinical examination, supplemented by case note review to establish visceral anomalies, and by radiological examination to look for subtle anomalies of the extracranial skeleton which may not produce clinical manifestations. The radiological examinations were compared to previous radiological studies to identify any changes, especially fusions, which developed after birth and so represent progressive disease.

The results obtained for each of the syndromes associated with FGFR mutations (Crouzon, Pfeiffer and Apert syndromes) will be compared with each other to establish the extent of overlap of the anomalies, as well as compared to the results of the investigation into Saethre-Chotzen syndrome (in which any extracranial anomalies have resulted from a different biological process).

The results of the radiographic examinations, presented in this thesis, have been used to establish protocols for the extracranial radiographic examinations, of a particular site, for each syndrome, to be drawn up, so as to improve the management of children with these syndromes in the future.

METHODS

The database of the Craniofacial Centre at Great Ormond Street Hospital was searched, to identify patients who attended between 1985 and 1995 with a diagnosis of Crouzon, Pfeiffer, Apert or Saethre-Chotzen syndromes. The diagnosis was principally made on the basis of their typical phenotypic appearance both by members of the Craniofacial team along with senior staff of the Clinincal Genetics department at Great Ormond Street Hospital. Atypical Crouzon and Pfeiffer phenotypes were included if the clinical findings in conjunction with the identification of the genotype by D.N.A. analysis, enabled them to confidently assigned to a particular syndrome by Clinical Genetics staff. Those cases where the diagnosis had not been established by either of these criteria were excluded from the study.

All case notes were reviewed to confirm each individual's medical history, and in particular to record all extracranial anomalies previously noted. Parental permission to perform a clinical examination of each patient at least once during the period March 1995 to April 1996 was taken. This examination was supplemented by a radiological examination of the extracranial skeleton. Cases which did not undergo clinical examination or did not have any extracranial radiographs taken were excluded from the study.

The radiographs of all cases were studied in conjunction with a Paediatric Radiologist who had an interest in skeletal dysplasia, to confirm the radiological findings. Any radiographs of inadequate or poor quality were discarded and not included in the results. All radiographs were examined for congenital anomalies of morphology and for

evidence of anomalous fusions, particularly at joints where evidence for synostosis was sought. Where serial studies had been undertaken the later radiographs were carefully studied for evidence of progressive fusion.

All results of clinical examination, radiological examination and case note review were recorded and are presented in Chapters Two, Three, Four and Five on the basis of the syndrome studied.

CHAPTER TWO

CHAPTER TWO

CROUZON SYNDROME

Sixty eight patients with Crouzon syndrome were identified from the records of the Craniofacial Centre at Great Ormond Street Hospital. Seventeen cases were excluded from the results because uncertainty regarding diagnosis existed, or the patients had not undergone any skeletal radiological examinations and could not be seen during the duration of the study. Forty four remaining cases had their diagnosis made on the basis of their phenotypic appearance after clinical examination (by the author). The features which were of particular importance were those of facial hypoplasia in the presence of cranial synostosis. All of these patients were also examined by the senior surgical staff of the Craniofacial Centre and a Geneticist who agreed with the diagnosis in each case.

The cases were aged from four months to twenty three years, with a median age of seven years, at the time of this review. There were thirty one males and twenty females. Cases 1 and 2, 11 and 12, 22 and 45, 43 and 44 were all siblings. Cases 9, 27, 42 and 46 also had affected parents. The remainder were thought to be the result of new mutations.

All forty four cases who attended Great Ormond Street Hospital during the period March 1995 - April 1996 were interviewed along with their parents to review the medical history and to perform a clinical examination including height and weight measurements. The height and weight measurements were compared to normal values (Tanner *et al.*, 1966), and to birthweight and any previously recorded values. This was supplemented by radiological examination and review of existing

medical and radiological records. The cases were assigned a number and the results of all the investigations recorded.

The genetic mutation had been recorded in twelve cases, (case no's 5,6,8,9,11,12,17,18,20,27,35 and 42). The radiological investigations undertaken in each of the cases are shown in Tables 2.1 and 2.2.

RESULTS

CLINICAL EXAMINATION

The clinical examination revealed loss of movement at the elbows in six cases, and is reported in greater detail later. There were no obvious deficiencies in height or weight records when compared to age and sex standards (Tanner *et al.,* 1966). The boys height ranged from the thirtieth to the ninetieth centile, their weights from the twentieth to the eightieth centile. The girls height and weight both ranged from the twentieth to the eightieth centiles. There was little difference between the centiles in birth weight and current weight both in boys and girls.

There were few associated anomalies reported from the history or identified from the case notes review. Case 46 had hypospadias and undescended right testes requiring orchidopexy, and case 24 had a congenital laryngeal cleft. Case 49 had eczema. No cardiovascular or gastrointestinal anomalies were reported. Cases 14 and 17 had undergone abdominal ultrasound examination to investigate persistent abdominal pain but these were both reported as normal.

TABLE 2.1 THE INVESTIGATIONS OF CROUZON SYNDROME

Case No.	Sex	Present Age	Cervical Spine	Hands	Others
1.	M	13	1	-	-
2.	M	15	1	-	-
3.	F	2	1	1	4
4.	M	12	2	1	-
5.	F	6	2	1	-
6.	F	7	1	-	-
7.	M	1	2	-	-
8.	M	15	1	1	-
9.	M	10	2	1	2
10.	M	4	1	-	-
11.	F	15	1	1	-
12.	M	14	1	1	-
13.	M	8	2	1	-
14.	M	9	2	1	1
15.	M	12	2	-	-
16.	M	7	2	1	4
17.	F	17	3	2	2
18.	M	6	2	1	3
19.	F	5	1	1	-
20.	M	15	1	-	1
21.	M	7	1	-	-
22.	F	4	2	1	-
23.	M	18	2	-	1
24.	F	8	2	1	2
25.	F	8	2	1	3
26.	F	14	1	-	-
27.	M	9	2	1	3
28.	F	2	1	-	-
29.	F	3	1	1	-
30.	M	17	1	1	3

Continued overleaf

TABLE 2.1 THE INVESTIGATIONS OF CROUZON SYNDROME
(continued)

Case No.	Sex	Present Age	Cervical Spine	Hands	Others
31.	F	8	2	1	-
32.	M	3	1	-	-
33.	M	5	1	-	-
34.	F	7	3	1	3
35.	M	6	1	1	3
36.	F	7	2	-	-
37.	M	8	2	1	2
38.	M	8	2	1	-
39.	F	16	1	-	-
40.	M	13	1	1	2
41.	M	7	1	1	1
42.	F	1	1	1	3
43.	M	4	1	1	3
44.	M	6	1	1	3
45.	M	7	1	1	1
46.	M	14	1	1	3
47.	F	10	1	2	6
48.	F	23	-	-	1
49.	F	8	1	1	1
50.	M	4/12	1	1	4
51.	M	4	1	1	-
Cases			50	35	26
Radiographs			72	37	65
Serial studies			20	2	2

All cases underwent clinical examination apart from case no's 3,6,15,26,33,39 and 48.

Other cases includes feet, elbows and shoulders which are shown in more detail in Table 2.2

TABLE 2.2 RADIOLOGICAL INVESTIGATIONS OF CROUZON SYNDROME

Case No.	Elbows	Shoulders	Feet	Others
1.	-	-	-	-
2.	-	-	-	-
3.	1	-	1	2
4.	-	-	-	-
5.	-	-	-	-
6.	-	-	-	-
7.	-	-	-	-
8.	-	-	-	-
9.	1	-	1	-
10.	-	-	-	-
11.	-	-	-	-
12.	-	-	-	-
13.	-	-	-	-
14.	-	-	-	1
15.	-	-	-	-
16.	1	1	1	1
17.	1	-	1	-
18.	1	1	1	-
19.	-	-	-	-
20.	1	-	-	-
21.	-	-	-	-
22.	-	-	-	-
23.	1	-	-	-
24.	-	-	-	2
25.	1	1	1	-
26.	-	-	-	-
27.	1	1	1	-
28.	-	-	-	-
29.	-	-	-	-
30.	1	1	1	-

Continued overleaf

TABLE 2.2 RADIOLOGICAL INVESTIGATIONS OF CROUZON SYNDROME
(continued)

Case No.	Elbows	Shoulders	Feet	Others
31.	-	-	-	-
32.	-	-	-	-
33.	-	-	-	-
34.	1	1	1	-
35.	1	1	1	-
36.	-	-	-	-
37.	1	-	1	-
38.	-	-	-	-
39.	-	-	-	-
40.	1	-	1	-
41.	-	-	1	-
42.	1	1	1	-
43.	1	1	1	-
44.	1	1	1	-
45.	1	-	-	-
46.	1	1	1	-
47.	2	1	2	1
48.	1	-	-	-
49.	-	-	1	-
50.	1	1	1	1
51.	-	-	-	-
Cases	22	13	20	6
Films	23	13	21	8
Serial studies	1	0	1	0

THE CERVICAL SPINE

Cervical spine studies (lateral and antero-posterior views) were available for fifty cases. Twenty of these had sequential studies, but no case had more than three sets of radiographs. Three radiographs were too poor to allow interpretation, leaving seventy one for study. C7 was not visualised in four of these cases, and also C6 in one case. The age at the time of the first radiograph ranged from two months to thirteen years, with the median age being six years.

Several types of anomalies were detected and included both congenital anomalies and fusion of the vertebrae. Cervical spine anomalies were seen in a total of twelve cases. These consisted of congenital anomalies in two cases, fusions in six cases and co-existing congenital anomalies and fusions in four cases.

There was evidence of fusion in a total of 10/50 (20%) cases. The levels affected, the age of each case at the time every radiograph was obtained, and the patterns of progression of the fusions are shown in Table 2.4. The solid bars represent vertebral body fusion and the clear bars represent fusion of the posterior elements (spinous processes and neural arches).

Eight cases exhibited fusions after the age of four years, while the remaining two cases were both aged less than two years. Both these cases (no's 34 and 36) developed further fusions on subsequent radiographs, demonstrating progressive fusion. An example is shown in Figures 2.1 and 2.2. Three further cases showed no evidence of fusion on their first radiographs, but had radiological evidence of fusion on a later radiographic study (cases 4, 5 and 15). The fusions were seen to

range in severity from affecting single intervertebral spaces to the production of block vertebrae affecting multiple intervertebral levels.

The levels most commonly affected were either C2/C3 or C5/C6 and examples are shown in Figures 2.1, 2.2 and 2.3. In a single case (no. 46) both levels were affected and this is shown in Figure 2.3. The pattern of fusion progression, at C2/C3 level, showed that the posterior elements underwent fusion before the vertebral bodies. At C5/C6 level the vertebral bodies underwent fusion before the posterior elements.

The congenital anomalies are shown in Table 2.3. "Butterfly" vertebrae are the most commonly seen anomaly, and an example is shown in Figure 2.5. These were found to occur either as isolated events in three cases or with multiple cervical vertebrae affected in two cases. The other anomalies seen were an enlarged neural arch and a hypoplastic vertebral body.

TABLE 2.3 THE CONGENITAL ABNORMALITIES OF THE CERVICAL SPINE IN CROUZON SYNDROME.

Anomaly	No. of cases	Levels exhibiting anomaly
"Butterfly" Vertebra	5	C3, 2 cases
		C4, 3 cases
		C5, 3 cases
		C6, 1 case
Large neural arch	1	C2
Hypoplastic body	1	C3

TABLE 2.4 THE CERVICAL SPINE FUSIONS SEEN IN CROUZON SYNDROME.

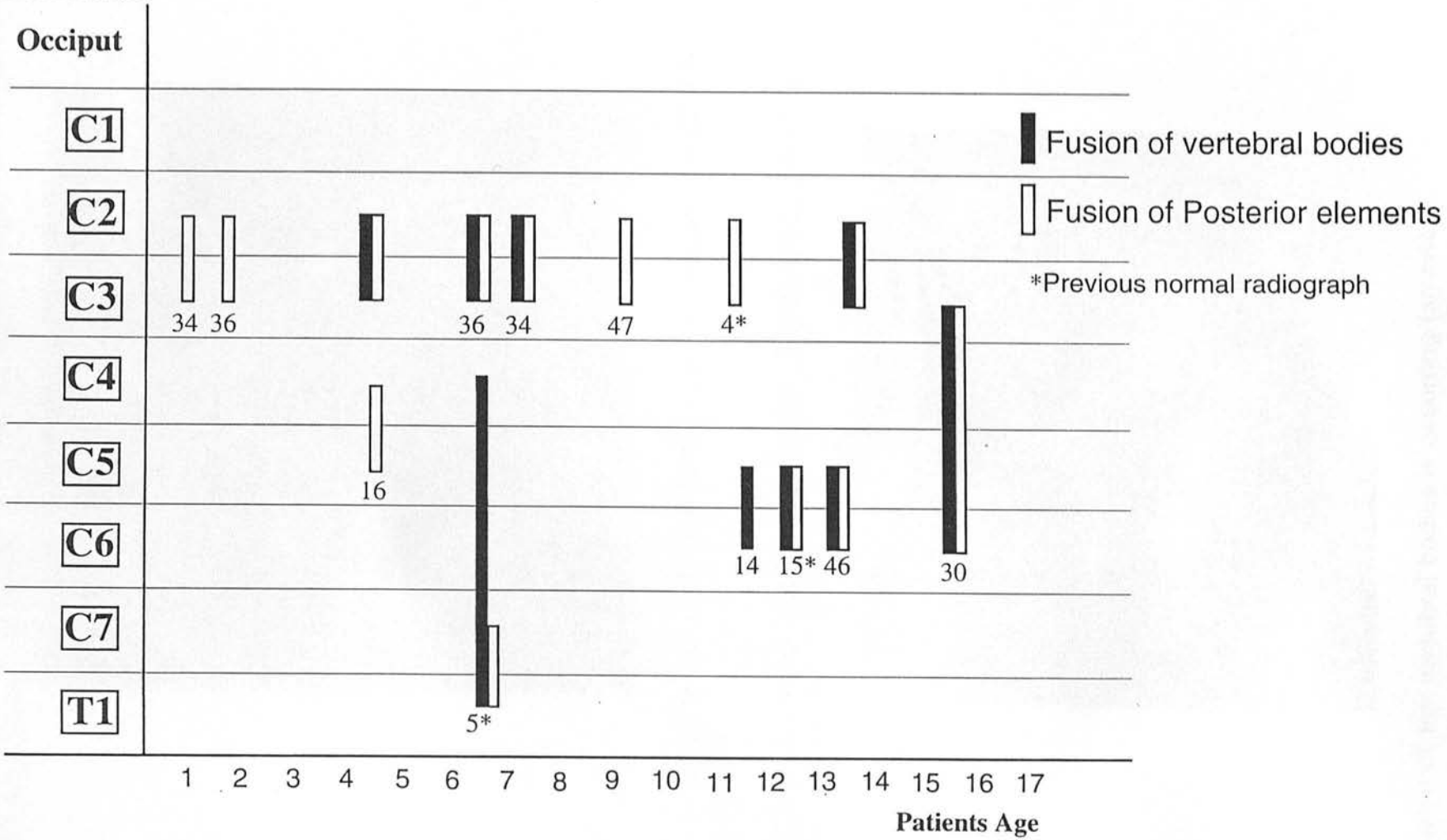
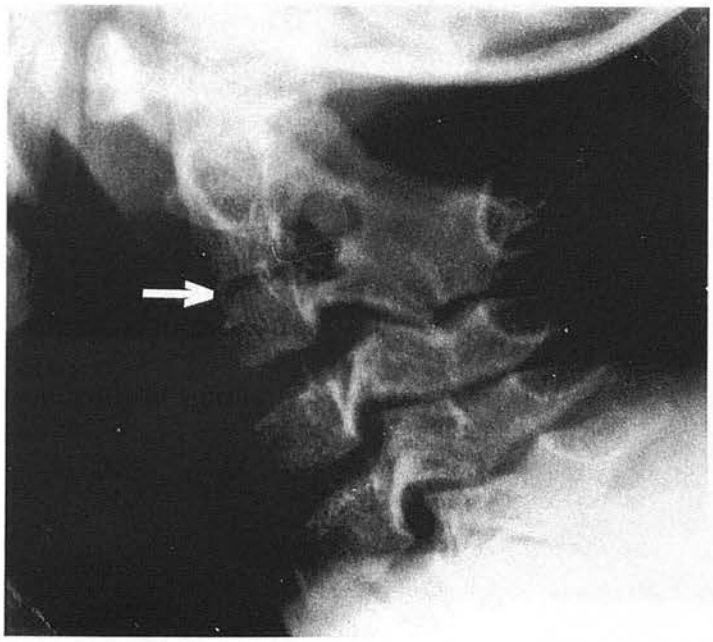


FIGURE 2.1 LEFT LATERAL CERVICAL SPINE RADIOGRAPH OF CASE 34 AGE THREE MONTHS

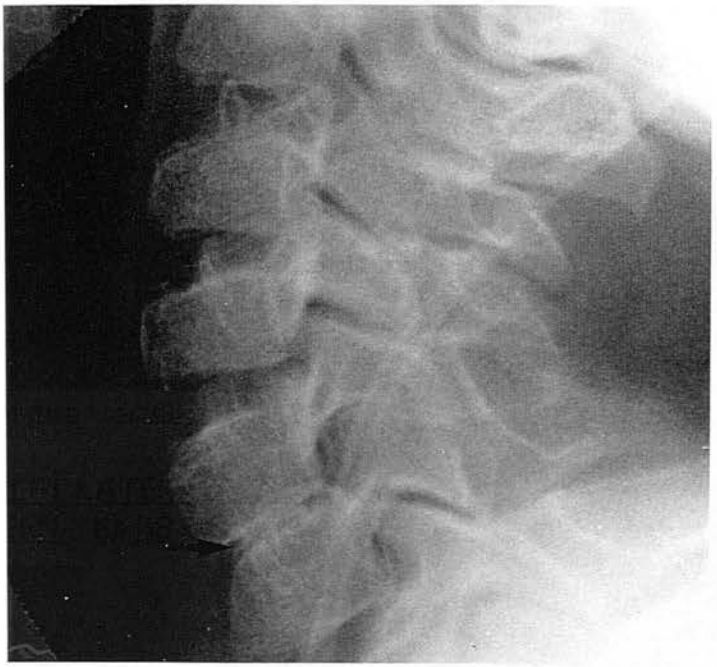
Fusion has already occurred of the posterior elements at C2/C3 (arrowed).

FIGURE 2.2 LEFT LATERAL CERVICAL SPINE RADIOGRAPH OF CASE 34 AGE SEVEN YEARS



Fusion of the vertebral bodies is occurring (arrowed).

FIGURE 2.3 LEFT LATERAL CERVICAL SPINE RADIOGRAPH OF CASE 15 AGE TWELVE YEARS

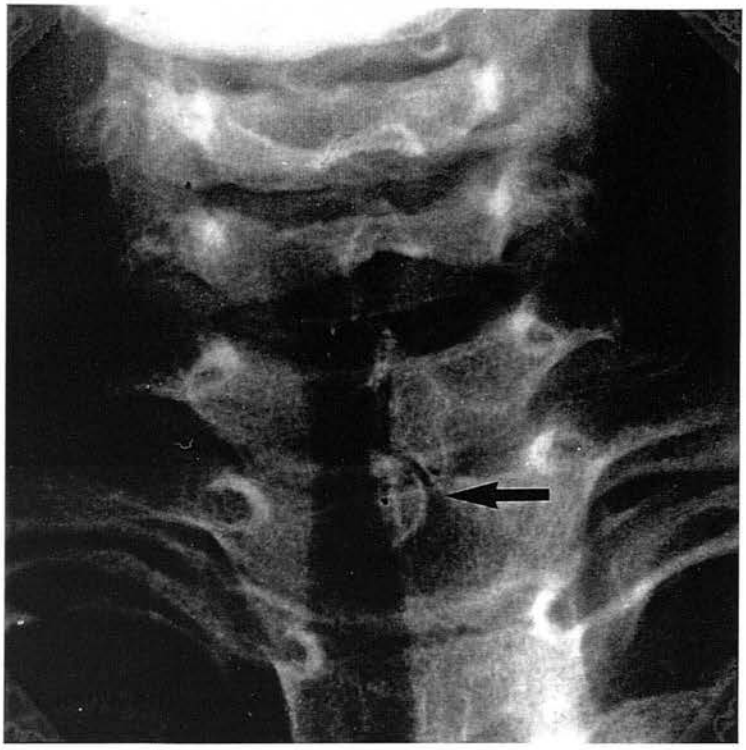


Early fusion of the vertebral bodies of C5/C6.

FIGURE 2.4 LEFT LATERAL CERVICAL SPINE RADIOGRAPH OF CASE 46 AGE FIFTEEN YEARS

Fusions of both vertebral bodies and posterior elements at C2/C3 and C5/C6 levels (arrowed).

FIGURE 2.5 ANTERO POSTERIOR RADIOGRAPH OF THE CERVICAL SPINE OF CASE 34 AGE THREE MONTHS



Butterfly vertebra (arrowed).

THE HANDS

The clinical examination was unremarkable in all cases with no loss of function or evidence of syndactyly.

Thirty five cases underwent radiographic examination of the hands. The time of first radiograph ranged from six months to seventeen years. Two cases (no's 17 and 47) underwent serial examination; there

was no evidence of progressive disease in either case. In twenty one cases the films were deemed to be normal in all respects. The remaining fourteen cases displayed several anomalies which are shown in Table 2.5.

Fusions affecting the carpal bones and pseudoepiphysis of the first metacarpal were the commonest anomalies. The carpal fusions affected just the bones of the distal row, and the fusion was always in a transverse direction rather than longitudinally. Two examples of carpal fusion are shown in Figures 2.6 and 2.7.

The bone age of each hand was compared to radiographic normals (Greulich and Pyle, 1959), and was within normal limits with one exception (case 45), which was two years delayed.

TABLE 2.5. ANOMALIES SEEN IN THE HANDS OF CROUZON SYNDROME.
35 cases, 21 normal. All cases symmetrical.

Anomaly	No. of cases
Clinodactyly	3
Phalangeal Ivory epiphyses	2
Pseudoepiphysis 1st Metacarpal	5
Hypoplastic 1st Metacarpal	1
Hypoplastic 4th Metacarpal	1
Carpal fusion	5
Bone age delay (greater than 2 years, Greulich and Pyle)	1

FIGURE 2.6 RADIOGRAPH OF BOTH HANDS OF CASE 30 AGE SEVENTEEN YEARS

Fusion of the Trapeziod and Capitate bilaterally (arrowed).

FIGURE 2.7 RADIOGRAPH OF BOTH HANDS OF CASE 41 AGE SEVEN YEARS

Fusion of the capitate and hamate bilaterally (arrowed).

THE FEET

Clinical examination of the feet was undertaken in forty four cases. Abnormal breadth of the big toe was noted during clinical assessment in four cases but there were no cases of syndactyly. All cases could wear normal footwear and had walked by fourteen months of age.

Radiological examinations were performed in twenty cases. The age at the time of the radiograph ranged from three months to seventeen years (with a median age of seven years). Four cases were normal (case no's 16, 27, 35 and 49). The remainder revealed a range of anomalies which were generally subtle but seen to occur at different sites within the bones of the feet. These anomalies included fusions affecting different sites, with the phalanges and the tarsal bones affected on occasion (see Table 2.6), and an example is shown in Figure 2.8. Case 47 demonstrated hypoplastic middle phalanges at age seven years, with no evidence of progressive fusion on a subsequent radiograph obtained at ten years of age.

The anomalies and their incidence are shown in Table 2.6. The first ray appeared to be the commonest site for anomalies with both the phalanges and the metatarsal occasionally determined to be abnormally broad on the radiographs. (The abnormalities breadth of the big toes determined radiologically did not always coincide with the abnormalities of breadth determined clinically). The distal and middle phalanges of the other toes were sometimes hypoplastic.

TABLE 2.6. RADIOGRAPHIC ANOMALIES OF THE FEET IN CROUZON SYNDROME.

20 cases, 4 normal. All cases symmetrical.

Anomaly	No. of cases
HALLUX	
Broad distal phalange	3
Broad proximal phalange	4
Fusion of the phalanges	2
TOES 2-5	
Hypoplastic distal phalanx	3
Hypoplastic middle phalanx	3
Absent middle phalanx	1
Phalangeal fusions	3
METATARSALS	
1st Metatarsal broad	4
1st Metatarsal pseudoepiphysis	4
5th Metatarsal pseudoepiphysis	1
TARSALS	
Dysplastic cuneforms	1
Fusion of Cuboid/cuneforms	2

FIGURE 2.8 RADIOGRAPH OF THE FEET OF CASE 30 AGE SEVENTEEN YEARS

Fusion of the middle and distal phalanges (arrowed) and tarsal fusions (cuboid/cuneform)

THE ELBOWS

Clinical examination of the elbows was performed in forty four cases and revealed limitation of movement (flexion/extension and pronation/suppination) in five cases who exhibited fixed flexion deformity (cases 17,23,34,37 and 42). In addition to these, case note review revealed that case 48 had fixed flexion deformity of 90 degrees. The severity of elbow anomalies in this case raises the possibility of a diagnosis of Antley-Bixler syndrome, in which early synostosis of the elbows during childhood is a recognised feature.

Radiographs were available for twenty two cases. They were normal in fourteen cases (case no's 3,9,16,18,20,25,27,35,40,44,45,46,47 and 50). Case 47 had serial studies available but all radiographs were normal. In the remaining cases a range of anomalies were seen and these are shown in Table 2.7. The ages of those with anomalies ranged from two years to twenty three years, (with a median age of ten years).

Subluxation of the radial head was the most common anomaly, an example of which is shown in Figure 2.9. The most severely affected case (no. 48) who has synostosis is awaiting elbow relacement, and the radiographs are shown in Figure 2.10. The enlarged medial epicondyle found in case 30 was a curious finding and is shown in Figure 2.11.

THE SHOULDERS

Clinical examination was performed in forty four cases and was unremarkable in all cases with no loss of movement detectable.

TABLE 2.7. RADIOLOGICAL ANOMALIES OF THE ELBOWS IN CROUZON SYNDROME.

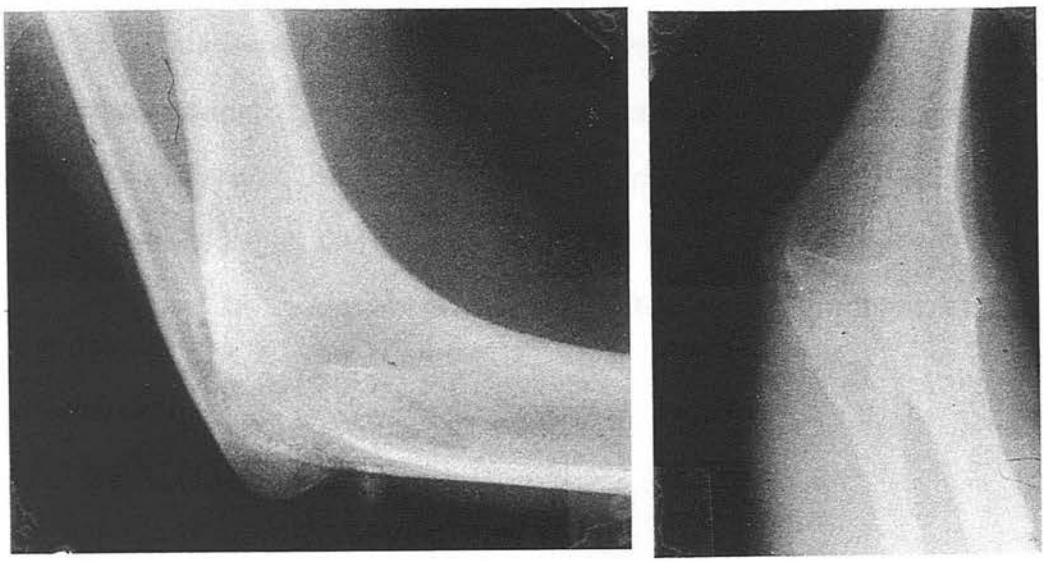
22 cases, 14 normal. All cases symmetrical.

Anomaly	No. of cases
Synostosis	1
Subluxation humero-ulnar joint	2
Subluxation radial head	5
Epiphyseal delay	4
Enlarged medial epicondyle	1
Total	13

FIGURE 2.9 LEFT LATERAL ELBOW RADIOGRAPH OF CASE 17 AGE SEVENTEEN YEARS

Note the dislocated radial head

FIGURE 2.10 ANTERO-POSTERIOR AND LATERAL RADIOGRAPHS OF THE LEFT ELBOW OF CASE 48 AGE TWENTY THREE YEARS



Severe synostosis of both the Humero-ulnar and Humero-radial joints (This extreme example could possibly be Antley-Bixler syndrome)

FIGURE 2.11 ANTERO-POSTERIOR RADIOGRAPH OF THE DISTAL HUMERUS OF CASE 30 AGE SEVENTEEN YEARS

Enlarged medial epicondyle

THE SHOULDERS (continued)

Thirteen cases (case no's 16,18,25,27,30,34,35,42,43,44,46,47 and 50) each had a single radiograph of both shoulders. The age at the time of the radiograph ranged from two years to seventeen years, (with a median age of eight years). All cases had symmetrical anomalies.

11/13 cases were normal. Case 42 had delayed epiphyses at age two years. Case 34 had small glenoid fosse with intraglenoid notching at age seven years.

OTHER RADIOGRAPHS

Cases 12 and 17 both underwent radiographic examination of the thoracic and lumbar spine at age three months. Case 12 was normal, while case 17 had a "Butterfly" vertebra at T6 in addition to scoliosis. A nuclear magnetic resonance study of the whole spine of case 5, at age three months, was normal. Cases 3, 24 and 47 underwent radiographic examination of the knees at ages three months, eight years and ten years respectively. Cases 3 and 47 were normal. Case 24 showed two relatively minor anomalies of flared metaphysis and absent tibial spines. Cases 3 and 16 had undergone radiographic examination of the ankles at age three months and five years respectively. Both examinations were normal.

Radiographs of the pelvis were available for cases 14 and 24 when aged twelve years and eight years respectively. Case 14 was normal but case 24 demonstrated bilateral hip joint subluxation with hypoplastic acetabula, cava valga and flared illiac wings.

Chest radiographs were examined for cases 2, 3, 17, 34 and 42 and were normal.

GENETICS

The mutations for twelve cases in this series had been identified and are shown in Table 2.8.

Seven different mutations were identified in these twelve cases and these were all of the FGFR 2 gene. No more than three cases had the same mutation, so the study of phenotypic variation is limited. 11/12 cases had mutations of the third immunoglobulin domain, which is where most of the mutation sites for Crouzon have been located.

However, Case 20 had a mutation in the first immunoglobulin domain and careful study was undertaken to search for phenotypic differences with the other cases. Clinical examination was unremarkable and radiographs of the cervical spine and elbows were all normal at age seventeen. Unfortunately, radiographs of the hands and feet were unavailable. On this limited information there was no evidence to suggest phenotypic difference in this case, although further studies are required to investigate this fully.

Cases 11,12 and 42 all had the Cys342Tryp amino acid substitution. The radiographs of the cervical spine and hands were all normal. However, case 42 underwent radiographs of the elbows, shoulders and feet all of which demonstrated anomalies. The elbows examination revealed dislocated radial heads, the shoulders delayed epiphyses and the feet hypoplastic distal and middle phalanges, thereby demonstrating significant extracranial manifestations. It is also notable that case 42 is still only two years old.

Cases 8,18 and 27 have the same amino acid substitution Ala344Gly, which has also been identified in Jackson-Weiss syndrome (Jabs *et al.*,

1994). These cases are all males aged six, nine and fifteen years respectively. Study of their extracranial manifestations revealed that they all had normal cervical spine and hands, elbows, and shoulders. Interestingly, the feet of case 18 had hypoplastic middle phalanges and broadening of the Ist metatarsal with a pseudoepiphysis and big toe phalanges, which have been described as clinical features of the Jackson-Weiss syndrome (Jackson *et al.,* 1976). These anomalies of the feet in case 18 are the only recorded extracranial manifestations in any of the three cases with this substitution.

Case 5 has the same mutation as a case of Pfeiffer syndrome (case 20 see chapter Three). Both these cases had similar craniofacial manifestations with severe maxillary hypoplasia and resultant respiratory difficulties. They both required major surgery to improve their airway as infants. With regard to the extracranial manifestations of case 5, the cervical spine demonstrated the severest progressive disease of any case diagnosed with Crouzon syndrome, and was similar to the anomalies seen in Pfeiffer syndrome. The first radiographs at age 2 months were normal but by age six years she had developed multiple vertebral body fusions creating a "block vertebra" affecting levels C4/C5, C5/C6, C6/C7, C7/T1(the posterior elements were additionally fused at the lowest level). However, her hands were radiographically normal. This compares with case 20, Chapter Three, who has the same amino acid substitution, and also exhibits anomalies of cervical spine (although less severe than case 5), but in addition her hands, feet, elbows and shoulders all had radiographic anomalies. Case 5 has normal hands but has not undergone investigation of the other sites. These limited findings both of the craniofacial and the cervical spine

demonstrate some overlap between these two phenotypes who share a common genotype. However, the radiographically normal hands of case 5, contrasts markedly with the anomalies at many other sites in case 20, Chapter Three, which supports the concept that these two cases belong to two different different syndromes.

TABLE 2.8 THE MUTATIONS IDENTIFIED IN CROUZON SYNDROME

Case No.	Mutation	Amino Acid change
5.	T1036 to A	Cysteine 342 to Serine
6.	C1052 to G	Serine 347 to Cysteine
8.	G1044 to A	Alanine 344 to Glycine
9.	T1020 to C	Tyrosine 340 to Histidine
11.	C1038 to G	Cysteine 342 to Tryptophan
12.	C1038 to G	Cysteine 342 to Tryptophan
17.	G1025 to C	Glycine 338 to Arginine
18.	G1044 to A	Alanine 344 to Glycine
20.	Ig1 Domain	Tyrosine 105 to Cysteine
27.	G1044 to A	Alanine 344 to Glycine
35.	T1020 to C	Tyrosine 340 to Histidine
42.	C1038 to G	Cysteine 342 to Tryptophan

DISCUSSION

A wide range of anomalies of the extracranial skeleton both of the morphological appearance and fusions have been demonstrated at many sites. The existence of some of these has been previously reported (Proudman *et al.,* 1994) but this is in marked contrast to a recent report which states that no limb abnormalities exist in this condition (Al-Quattan and Al-Husain, 1996).

The unremarkable height and weight measurements contrast with the findings of a large series reported by Kreiborg in 1981, which found reduced final height in females and a single earlier report associating the condition with short stature in a male (Field *et al.,* 1991). The differences may be due to the fact that these cases studied have not yet reached skeletal maturity, but given the lack of other data there is little evidence to suggest that there is a predisposition to short stature associated with the condition.

There were few non-skeletal associated anomalies. Mitral valve prolapse, gastro-oesophageal reflux, and anal anomalies have all been reported (Proudman *et al.,* 1994). Acanthosis nigricans has been reported to be associated with the condition (Reddy, 1985). However, no cases were detected in this study. This association is now known to occur in Crouzon phenotypes which result from FGFR 3 gene mutations (Meyers *et al.,* 1995). This suggests that there are none of these particular genotypes in this population.

THE CERVICAL SPINE

Radiological abnormalities of the cervical spine were seen in 12/50 cases. This can be compared to the incidence in the general population which has been reported to be 0.5% to 3% (Shands and Bundens 1956; Gray *et al.,* 1964).

Cervical fusions were demonstrated in 10/50 cases (20%) in this series, which is lower than previously reported series which range from 32% to 39% (Kreiborg, 1981; Golabi *et al.*, 1984). This difference could be accounted for by the fact that unlike previous reports, this population consists of children and since there is evidence to suggest that these fusions are progressive (progressive fusion has been demonstrated in five cases (no's 4,5,15,34 and 36), then not all possible fusions may have had sufficient time to become radiologically evident.

The pattern of fusions is also notable as both C2/C3 and C5/C6 are almost equally affected. This finding is in contrast with all previous reports of Crouzon syndrome which have concluded that C2/C3 alone is the most commonly affected level (Kreiborg, 1981; Golabi *et al.,* 1984; Hemmer *et al.,* 1987; Proudman *et al.,* 1994), The finding also contrasts with the report that C2/C3 is the most common site for fusion in the general population (Brown *et al.*, 1964). This again may reflect the method of diagnosis of the condition, especially as C2/C3 is the level affected by fusion preferentially in both Pfeiffer and Saethre-

Chotzen syndromes. Additionally, the fact that cervical spine radiographs have been used in this study, as opposed to lateral cephalograms, which only provide limited views of the upper cervical spine, may also be a contributing factor. Case 46 with fusion occurring at both C2/C3 and C5/C6 is interesting, as fusion at both of these sites has only once been previously reported (Kreiborg, 1981).

The pattern of fusions is notable in that both the vertebral bodies and posterior elements are similarly affected by fusions. This too contrasts with earlier studies which showed a marked preference for vertebral body fusion (Kreiborg, 1981; Proudman *et al.,* 1994). In this series two cases (no's 34 and 36) had undergone serial radiographic examinations and showed fusion of the posterior elements at C2/C3 before fusion of the vertebral bodies. A further case (no. 4) had only posterior fusion at this level suggesting that at the C2/C3 level fusion of the posterior elements precedes vertebral body fusion. Curiously, this pattern was not repeated at the C5/C6 level. In two cases (no's 5 and 14) there was only evidence of vertebral body fusion. This apparent difference in fusion patterns within the cervical spine, in this condition, is interesting but a larger series will be required to establish the validity of this finding. The reason for this differential pattern of progressive fusion is, currently, unclear.

In assessing the significance of anomalies other than fusions, the finding of "Butterfly" vertebrae in 5/50 cases (10%), is similar to the findings of an earlier but much smaller study of Crouzon syndrome (Hemmer *et al.,* 1987). This particular congenital malformation appears to be more common in Crouzon syndrome rather than the other craniosynostosis syndromes. Only one "Butterfly" vertebra was seen in

the cervical spines of those with Pfeiffer syndrome and no cases affecting those with Apert or Saethre-Chotzen syndrome. It is notable that those with fusions commonly had pre-existing "Butterfly" vertebrae, although the affected levels do not exactly coincide, and it has been proposed that this anomaly predisposes to vertebral fusion in the general population (Muller *et al.,* 1986). While C3 and C5 are frequent sites for both of these anomalies to occur, C4 is an unusual level to develop fusion.

The finding of an enlarged neural arch has been found more commonly in Saethre-Chotzen syndrome, although its significance is unclear. Finally, the absence in this series of a 'high atlas', which has been reported as occurring in several cases within a series (Hemmer *et al.,* 1987; Proudman *et al.,* 1994), is notable, although the reason is unclear.

The clinical significance of these fusions remains uncertain. No direct adverse clinical effects have been recorded in this series as a result of fusion. However, spontaneous hemiplegia in a twelve year old associated with cervical fusions has been reported in this syndrome (Proudman *et al.,* 1994), and this report underlines that serious consequences of cervical fusion although rare, can occur. However, it is possible that the fusions may have a more common but subtle influence by altering head posture (this is discussed in more detail in Chapter Six).

THE HANDS

The absence of syndactyly in this series is in keeping with all previous reports except two (Dodge *et al.,* 1959; Proudman *et al.,* 1994).

A review of all the photographs in the report by Dodge *et al., (*1959) demonstrating the head, hands and feet, suggests that this may have been an example of Pfeiffer syndrome, (which was not recognised as a separate entity at that time). The report by Proudman *et al., (*1994) does not include any photographs, but the other reported hand anomalies suggest that their series may also have included atypical Pfeiffer phenotypes. The absence of any other reports together with the findings of this study suggests that syndactyly can only occur rarely in association with Crouzon syndrome, if at all. The finding of anomalies in fourteen cases in this series was surprisingly high given the few previously published reports. Minor skeletal anomalies consisting of clinodactyly, hypoplastic middle phalanx of the little finger and generalised brachydactyly have been reported in 5/59 cases (Proudman *et al.,* 1994), but it was not reported how many of these anomalies were diagnosed after radiographic examination. In another series of fifteen hand radiographs of Crouzon syndrome, there were no obvious abnormalities, but metacarpophalangeal pattern profile analysis revealed subtle differences from normal controls (Kaler *et al.,* 1982).

The principal radiographic finding of the 5/35 cases who exhibited carpal fusions, has not been previously recorded in Crouzon syndrome and there is no doubt regarding the diagnosis in any of these cases. The unremarkable clinical findings are in keeping with previous reports (Gorlin *et al.,* 1990).

Interestingly, the fusion of the capitate to the hamate, the hypoplastic fourth metacarpal, clinodactyly and delayed bone age are all anomalies seen in Pfeiffer syndrome (see Table 3.6). The presence of pseudoepiphyses, particularly affecting the first metacarpal, appears to

be a new association with Crouzon syndrome. However, these anomalies are found within the normal population, occurring at an incidence of 4 - 20% (Poznanski, 1972), and so the incidence (5/35 cases) in this series requires caution in interpreting their significance. Ivory epiphyses are commonly found associated with the distal phalanges in the normal population with an incidence of 4·4 - 8·4% (de Itturzia and Tanner, 1969). They may also be associated with retardation in skeletal maturation (Kuhns *et al.*, 1973) and in epiphyseal dysplasias (Poznanski, 1972). However the finding of only a single case of delayed bone age compared with radiological standards (Greulich and Pyle, 1959), suggests that skeletal delay is not a feature of Crouzon syndrome in this series.

The finding of carpal fusions in the hands shows that the hands may be affected as part of the syndrome, and clearly contradicts the view that there are no limb abnormalities in Crouzon syndrome (Al-Quattan and Al-Husain, 1996).

THE FEET

No difficulties with walking or footwear were reported. Previous reports of anomalies of the feet are confined to a single report of syndactyly (Dodge *et al.*, 1959), a single example of calcaneocuboid fusion and symptoms of pain sufficent to warrant surgical intervention (Craig and Goldberg, 1977). Five further cases of Crouzon had undergone radiography of their feet but were all normal (Craig and Goldberg, 1977). It has also been reported that fifteen cases had no

signs of foot anomalies, although it is unclear from the report whether they had undergone formal radiological examination (Kaler *et al.,* 1982).

The results of this study in which 16/20 cases had a demonstrable skeletal anomaly is remarkably high and contrasts with the absence of soft tissue anomaly (syndactyly) in the series. The single earlier report of syndactyly of the feet (Dodge *et al.,* 1959) has features suggesting that this may have been an example of Pfeiffer syndrome. The conclusion is the same as the hands, syndactyly is an exceptional occurrence, if it ever does exist as part of the syndrome.

The finding of so many skeletal anomalies in this series compared to previous reports suggests that these anomalies are more common in the Crouzon population. However, because they are mild and do not produce symptoms, few patients undergo the radiographic examinations that would reveal such anomalies. In addition as the radiographic signs are often subtle, careful examination is required to identify minor anomalies.

The anomalies which have been demonstrated include two further cases of calcaneocuboid fusion, which has been reported previously (Craig and Goldberg, 1977). However, the phalangeal fusions identified in five cases and the increased broadening of the first metatarsal and phalanges of the hallux are new associations. The increased broadening of the big toe is classically described in Pfeiffer syndrome. Knowledge of its occurrence in Crouzon syndrome is important when attempting to reach a diagnosis of Pfeiffer and Crouzon syndromes on the basis of clinical examination alone.

ELBOWS

There are few published series concerning anomalies of the elbow in Crouzon syndrome. Limitation of elbow movement in a series of fifty nine cases has been reported to occur with an incidence of 18% (Proudman *et al.,* 1994). Their series which was a restrospective review found clinical symptoms recorded in the notes with equal numbers of symmetrical and unilateral involvement, but radiographs had only been obtained for six cases. These demonstrated synostosis in one case and subluxation or dislocation in the rest. Interestingly the case with elbow synostosis was reported to have fixed flexion deformities of the shoulders, hips and knees. Clinical stiffness has been reported in 16% of a series of 61 cases (Kreiborg, 1981) and this included radial head subluxation in 2/61 cases. Isolated case reports of stiffness, subluxation of the radial head and synostosis have been reported (Polinelli and Imolda, 1963; Baldwin, 1968; Kushner *et al.,* 1972). Cubitas valgus has also been reported in a single case (Gorlin *et al.,* 1990).

8/22 cases who were radiographed exhibited some radiological anomaly. Five of these had radiological subluxation or synostosis affecting the elbow. It is notable that within the group who had anomalies there were three cases who had mild clinical manifestations (which subsequently demonstrated radiological anomalies) who were unaware of these prior to their examination. This raises the possibility that the other cases not undergoing radiographic examination, who were asymptomatic, may not have been radiographically normal. These findings confirm the earlier reports that anomalies of the elbows are not

uncommon in Crouzon syndrome, but further prospective studies will be required to establish the exact incidence.

THE SHOULDERS

Clinical examination of the shoulder was normal in all those examined. One case complained of intermittent pain but subsequent clinical and radiological examination was unremarkable.

The only previous report of anomaly of the shoulders in Crouzon syndrome was that of fixed flexion deformity and was reported in association with synostosis of the elbows (Proudman *et al.,* 1994). In this series only 2/13 cases had radiological evidence of any anomaly and both of these were minor. Interestingly both of the anomalies (small gleniod fosse and delayed epiphyses) are also seen in Apert and Pfeiffer syndromes, see Chapters Three and Four. In conclusion it would therefore appear that anomlies of the shoulder in Crouzon syndrome are rare.

OTHER VIEWS

The finding of a "Butterfly" vertebra in the thoracic region is interesting given that this congenital anomaly was the most commonly seen congenital anomaly of the cervical vertebrae in this series. This case (case 17) had three cervical spine studies, the last at age seventeen years, with no congenital anomalies or fusions seen, which

contrasts with the finding in the cervical spine when all cases with "Butterfly vertebrae" were associated with fusions.

The other cases undergoing examination of the lower spine were normal. However, this included case 5 which developed fusions at multiple levels of the cervical spine by the age of five years. The significance of these findings, with the small numbers studied preclude any assessment of their significance. Further study of the lower spine is required.

The finding of pelvic anomalies, although just in a single case, has not been previously reported. This contrasts with the absence of rib and sacral anomalies in this series which have been previously reported (Golabi *et al.,* 1984). No radiological anomalies of the knees could be identified in these cases, which were all normal, including the bone age (Pyle and Hoerr, 1969).

GENETICS

The twelve cases had a total of seven identified mutations, with no more than three cases for any genotype. This limited the study for phenotypic variation, within the same genotype. The commonest reported mutations identified for Crouzon syndrome worldwide are Ala344Ala, Cys342Tyr and Tyr340His (Cohen, 1995). It is notable that this population contained no examples of two of the commonest genotypes.

The identification of the same mutation of Cys342Tryp in three cases revealed marked differences in the extent and severity of the

extracranial manifestations of the syndrome, between case 42 and cases 11 and 12, suggesting that wide phenotypic variation can occur. However, cases 11 and 12 are siblings so the similar manifestations in their cases is perhaps not surprising.

This finding contrasts with the absence of phenotypic variation in the group with the Ala344Gly mutation (cases 8,18 and 27). In these cases there were no extracranial anomalies of the cervical spine or hands and only one of these three cases (case 18) exhibited anomalies affecting the feet. The identification of these three cases of Crouzon syndrome with the Ala344Gly mutation, (which also occurs in Jackson-Weiss syndrome (Jabs *et al.,* 1994), is of particular interest. The Jackson-Weiss syndrome is also a complex craniosynostosis syndrome. All members originally described belonged to a single extended family and had very variable clinical features. In addition to the craniosynostosis, midface hypoplasia and foot anomalies are the most consistent features (Jackson *et al.,* 1976). Although there were anomalies of the feet in case 18, there is little evidence to suggest phenotypic overlap.

Case 5 which has the Cys342Ser mutation, a genotype which can also be found in Pfeiffer syndrome phenotypes (Reardon, personal communication), is interesting. The diagnosis has been based on the phenotypic appearance despite identification of the genotype. The craniofacial manifestations include severe maxillary hypoplasia. The pattern of cervical fusions is the severest of any of the forty seven cases who underwent radiograghic examination of the cervical spine. The production of a "block vertebra" is a feature often seen in those with Pfeiffer syndrome. Conversely, the levels affected are all the lower cervical spine, and curiously C2/C3, which is the most commonly

affected level in Pfeiffer and Crouzon syndrome is spared. However, the hands were completely normal which is unusual in Pfeiffer syndrome. The significance of these diverse findings in this single case are difficult to assess, but this case undoubtedly has severe manifestations for Crouzon syndrome and has features similar to a Pfeiffer phenotype, which complicates the diagnosis. Study of further genotypes with the Crouzon phenotype will be required to establish whether the pattern of manifestations associated with this particular mutation consistently produce extracranial anomalies similar to those seen in Pfeiffer syndrome.

CONCLUSIONS

The extracranial manifestations of Crouzon syndrome in the group of patients in this study are much more widespread than previous reports would suggest, and include carpal fusions in the hands, radial head subluxation of the elbows and multiple anomalies found in the feet. However, the low incidence of anomalies recorded at the shoulders contrasts with the findings in both Apert and Pfeiffer syndromes (Chapters Three and Four) .

The widespread distribution of anomalies in this series could be explained by differences in this population studied compared to those used in earlier studies. It is interesting to note that no example of two of the commonest genotypes (Cohen, 1995) has been identified in this population.

Additionally, there are also some differences in age and sex ratio's to previous series. Nevertheless it is important to remember that these manifestations are often subtle and only identifiable radiologically, and so even if present may not have been searched for in previous studies.

The additional and unexpected findings in the limbs have to be reconciled with the finding that the incidence of cervical fusions at 20%, is less than previously published reports which range from 30-39% (Kreiborg, 1981; Proudman *et al.,* 1994). This is probably due to several factors. The differences due to the method of diagnosis will result in this sample containing less atypical examples of other syndromes (Anderson *et al.,* 1996a), which have a higher incidence of cervical fusions. Also the inclusion of children rather than just adults in this study, may mean that fusions which progress with time were not yet evident.

The new finding of carpal fusions, demonstrates that the hands can be affected in Crouzon syndrome, despite recent reports to the contrary (Reardon and Winter, 1995; Al-Quattan and Al-Husain, 1996). The feet and elbows too have demonstrated anomalies at a higher incidence than previous reports have suggested (Craig and Goldberg, 1977; Proudman *et al.,* 1994). However, this was not repeated for the shoulder or any of the other joints investigated, where anomalies were rare and when present were minor.

The range of extracranial anomalies within the fifty one cases is marked. There was no clear association between the severity of the craniofacial manifestations and the presence or severity of extracranial

anomalies. This means that as many extracranial anomalies are only detected radiographically, there is no way of predicting who will have these anomalies from clinical examination or from the severity of the craniofacial manifestations.

The available evidence suggests that there may be marked variations within the same phenotype, although as more genotypes are identified it will become possible to clarify this as well as to investigate whether there are patterns of malformation associated with particular genotypes. The evidence for overlap with Jackson-Weiss syndrome and Pfeiffer syndrome in those with common genotypes is equivocal, but stronger evidence comes from the case with the Pfeiffer genotype who has craniofacial and cervical spine findings which are very similar to those with Pfeiffer syndrome. More cases will be required to clarify this.

A large number of sites in which anomalies (although minor) have been seen, does not correspond to all sites where FGFR 2 occur. There were no visceral anomalies despite the presence of these receptors in the kidney, lungs and liver (Johnson and Williams, 1993).

The types of anomalies which occur are mostly in sites (cervical spine, hands, elbows and feet) similar to those affected in both Apert and Pfeiffer syndrome, both of which can result from FGFR 2 mutations. The shoulders and knees are interesting exceptions, and the reasons for the differences at these sites are unclear.

Long term follow up of these cases as they undergo skeletal maturity will determine if any more develop fusions, and if those with evidence of existing fusions undergo progression. The follow up may also determine whether symptoms eventually result at any of these affected sites.

Overall these results enhance the existing knowledge of Crouzon syndrome by demonstrating an increased number of sites with anomalies, all as a direct effect of a single mutant gene. The method by which the disease process produces deformities only in particular sites, when the underlying mutation affects a receptor which is widely distributed throughout the body is unclear, but will be discussed later (Chapter Six). The identification of many mutations now known to be responsible for the syndrome leads to the question as to why so many different mutations can produce the same phenotype, while the same mutation, of the same receptor, can produce different phenotypes. Although the question will probably be answered by molecular biologists, the solution to this fascinating conundrum may be aided by knowledge of the full extent of the disease process in this condition.

CHAPTER THREE

CHAPTER THREE

PFEIFFER SYNDROME

Thirty cases of Pfeiffer syndrome were identified from the records of the Craniofacial Centre at Great Ormond Street Hospital. Five cases had only been seen once and no extracranial radiographs had been taken. As they were unable to be reviewed clinically during the period of the study these five cases were excluded. Twenty three cases, all of whom had their diagnosis made on the basis of their phenotypic appearance after clinical examination (by the author), were included. The features which were of particular importance were cranial synostosis, midface hypoplasia, and clinically enlarged thumbs and big toes. These patients were also examined by senior surgical staff of the Craniofacial Centre and a Geneticist who agreed with the diagnosis in each case.

The cases aged from two months to seventeen years at the time of this review. There were ten males and fifteen females. Cases 18 and 22 were siblings. The remaining cases were thought to be the results of new mutations. Two of cases died (cases 1 and 23). Case 23 died of a respiratory infection aged eight months, and case 1 died intraoperatively following the division, extracranially, of anomalous vessels draining the intracerebral venous circulation. Although clinical examination was not possible, photographic records confirm that these two cases had characteristic phenotypic features, so the results of their radiological examinations are included.

The remaining twenty three cases who attended Great Ormond Street Hospital during the period March 1995 - April 1996 were interviewed along with their parents to review the medical history and to perform a

clinical examination (including height and weight measurements). The height and weight measurements were compared to normal values (Tanner *et al.,* 1966), to birthweight and to any previously recorded values. This was supplemented by radiological examination, and by review of existing medical and radiological records. The cases were each assigned a number and the results of all the investigations recorded.

The details of the different radiological investigations performed for each case are summarised in Tables 3.1 and 3.2.

RESULTS

CLINICAL EXAMINATION

The clinical examination of the locomotor system was unremarkable apart from loss of movement at the elbows in seven cases (see below). There were no obvious deficiencies in height or weight when compared to age and sex standards (Tanner *et al.,* 1966). The boys height ranged from the twenty-fifth to the seventy-fifth centile, and weights from the twenty-fifth to the ninetieth centile. The girls height ranged from the twenty-fifth to the ninetieth centile, and weights from the tenth to the ninetieth centile. There was little difference between the centiles in birth weight and current weight in both boys and girls.

Visceral anomalies reported from history and case note review revealed coarctation of the aorta, patent ductus, small ventricular septal defect in case 23, and an ectopic anus in case 6. Case 14 had a congenital inguinal hernia, underwent a fundoplication for persistent gastro-oesophageal reflux and was fed via a gastrostomy.

TABLE 3.1 THE CASES AND THEIR PRIMARY RADIOLOGICAL INVESTIGATIONS

Case No.	Sex	Current Age (years)	Cervical Spine	Hands	Other
1.	F	D	3	1	N
2.	F	7	2	1	Y
3.	M	17	2	3	Y
4.	F	1	2	1	Y
5.	F	9	1	1	Y
6.	F	11	1	1	Y
7.	F	7	2	1	Y
8.	M	17	1	1	Y
9.	F	7	1	-	N
10.	F	4	2	2	Y
11.	M	13	1	1	Y
12.	M	5	3	3	Y
13.	F	4	3	1	Y
14.	M	5	3	1	Y
15.	M	1	2	2	Y
16.	M	14	2	2	Y
17.	M	3	2	-	N
18.	M	14	1	1	Y
19.	F	14	3	1	Y
20.	F	5	2	1	Y
21.	F	1	2	2	Y
22.	F	16	1	1	Y
23.	F	D	-	-	Y
24.	F	6	-	-	Y
25.	M	2/12	1	1	Y

Totals

Patients	23	21
Films	43	29
Serial Studies	15	6

Cases 1,9,23 and 24 did not undergo clinical examination.

Cases 1 and 23 died before the start of this study and this is shown by D in the current age column.

TABLE 3.2 OTHER RADIOLOGICAL INVESTIGATIONS

Case No.	Feet	Elbows	Shoulders	Knees
1.	-	-	-	-
2.	1	1	2	-
3.	1	-	1	-
4.	1	1	1	1
5.	1	-	-	-
6.	1	1	1	-
7.	1	1	1	1
8.	1	1	-	-
9.	-	-	-	-
10.	2	1	-	-
11.	3	-	-	-
12.	1	-	1	-
13.	1	1	1	-
14.	1	1	1	1
15.	2	2	2	2
16.	1	1	1	-
17.	-	-	-	-
18.	1	1	1	-
19.	1	2	2	1
20.	1	1	1	-
21.	1	2	1	1
22.	1	1	1	-
23.	1	-	-	-
24.	2	-	-	-
25.	1	1	1	1
Total				
Cases	22	16	16	7
Films	27	19	19	8
Serial studies	4	3	3	1

THE CERVICAL SPINE

Cervical spine studies (lateral and anterior-posterior views) were available for twenty three cases. Fifteen of these had sequential studies available, but no patient had more than three sets of radiographs. One film was discarded as the film was deemed too poor to allow proper assessment. In six of the radiographs C7 was not included, and C6 not visualised in one case. The age of the cases at the time of the first radiograph ranged from two months to seventeen years, with the median age being seven years.

Nine of the twenty three cases who underwent radiographic examination of the cervical spine (no's 3,5,11,12,13,17,21,22 and 25) had at least one radiograph which was considered normal. However, cases 12 and 13 developed fusions on subsequent radiographs.

Fusions affecting the cervical spine were seen in 16/23 cases (70%). These fusions were demonstrated to be progressive in the radiographs of eleven of the fourteen cases who underwent sequential studies (no's 1,2,4,7,10,12,13,15,16,19 and 20). An example is shown in Figures 3.1 and 3.2. Fusions were seen to affect the vertebral bodies, the posterior elements or both of these. All levels were affected by fusions on occasion although C2/C3 was clearly the most commonly affected level with 10/16 affected cases exhibiting fusions. The ages of the cases and the positions of the fusions are shown in Tables 3.4 and 3.5. These two tables divide the cases depending on the presence of progressive fusion on serial radiographs. Table 3.4 shows cases who had a single radiographic examination and three cases who underwent serial studies but without evidence of progressive fusion (no's 3,14 and 17). Table 3.5 shows the development of the progressive fusions in

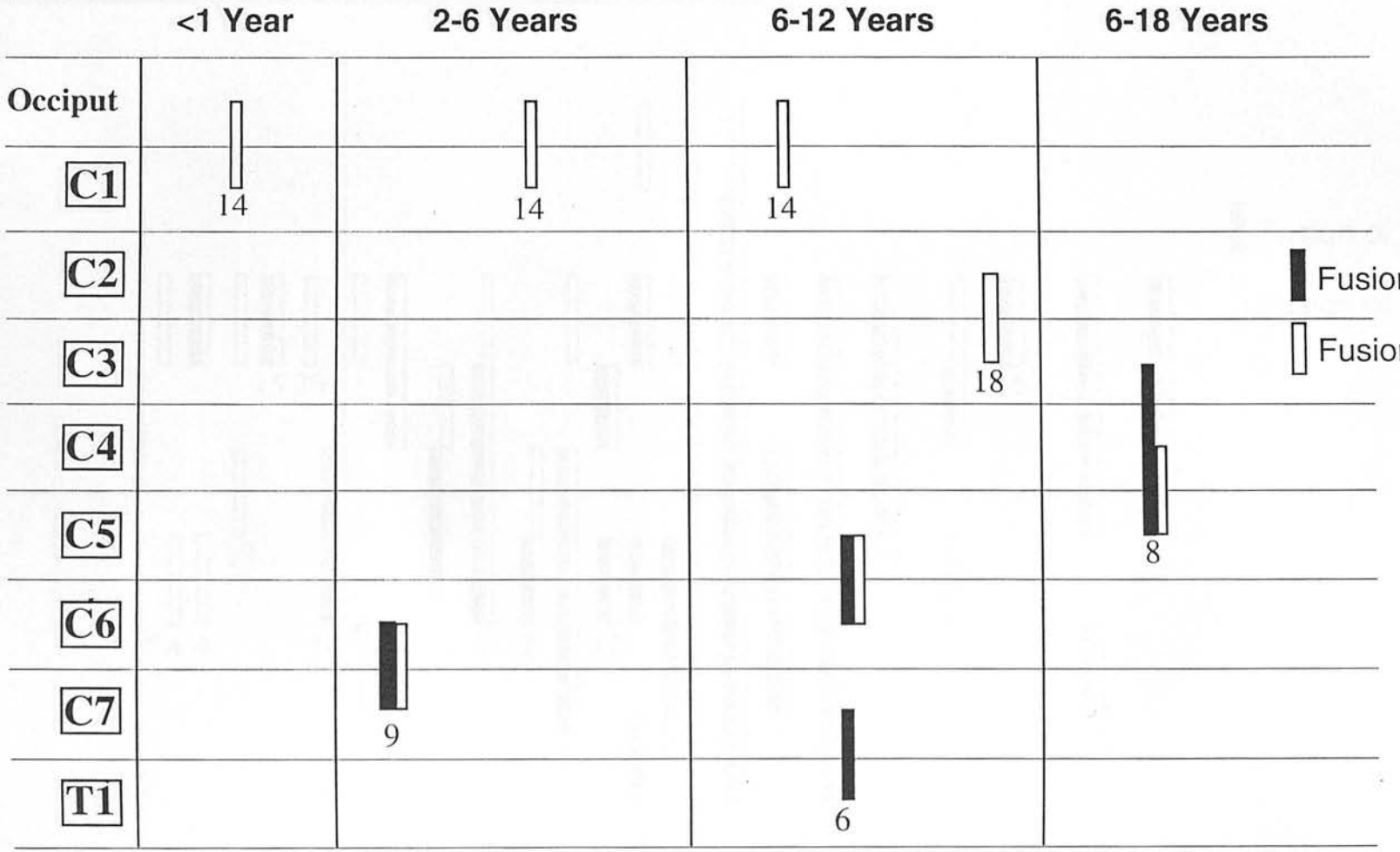
relation to the age at the time of the radiograph, in each of the affected eleven cases. These tables also show the block fusions involving more than one adjacent vertebra at a single level which were observed in eight cases, and involved a variety of levels. An example of this shown in Figure 3.3.

Other congenital anomalies were observed, with hypoplasia of C1 vertebra being the most common, occurring in 9/23 cases. It is notable that in all but one case, where there was a hypoplastic C1, there were, (or subsequently developed), fusions. The exception was case 3 who is already skeletally mature and so unlikely to fuse. "Butterfly" vertebrae and hemivertebrae were also seen and noted to affect different levels, these too were found in association with fusions. The incidence of these congenital anomalies and their levels are recorded in Table 3.3.

TABLE 3.3 CONGENITAL ANOMALIES OF THE CERVICAL SPINE
23 cases

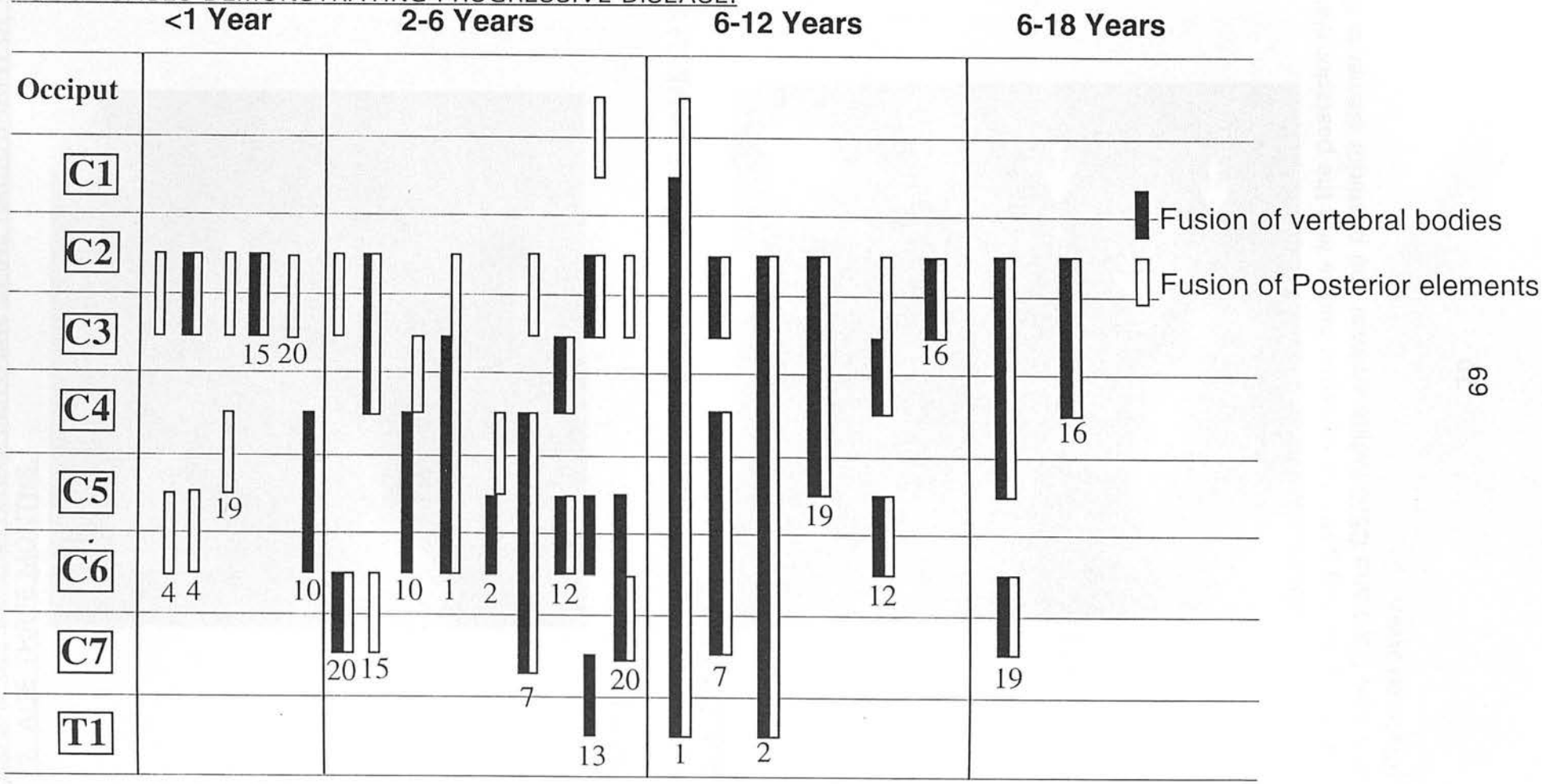
Anomaly	Level	No. of cases
HYPOPLASTIC NEURAL ARCH	C1	9/23
	C4	1/23
BUTTERFLY VERTEBRA	C3	1/23
	C4	1/23
HEMIVERTEBRA	C4	1/23
	C5	1/23
	C7	1/23

TABLE 3.4 CERVICAL SPINE FUSIONS IN PFEIFFER SYNDROME IN NON-PROGRESSIVE CASES DEMONSTRATING LEVELS AFFECTED



17, 21 No fusions. 3,17,25 No fusions. 5, 11 No fusions. 3, 22 No fusions.

TABLE 3.5 CERVICAL SPINE FUSIONS IN PFEIFFER SYNDROME IN THOSE CASES DEMONSTRATING PROGRESSIVE DISEASE.

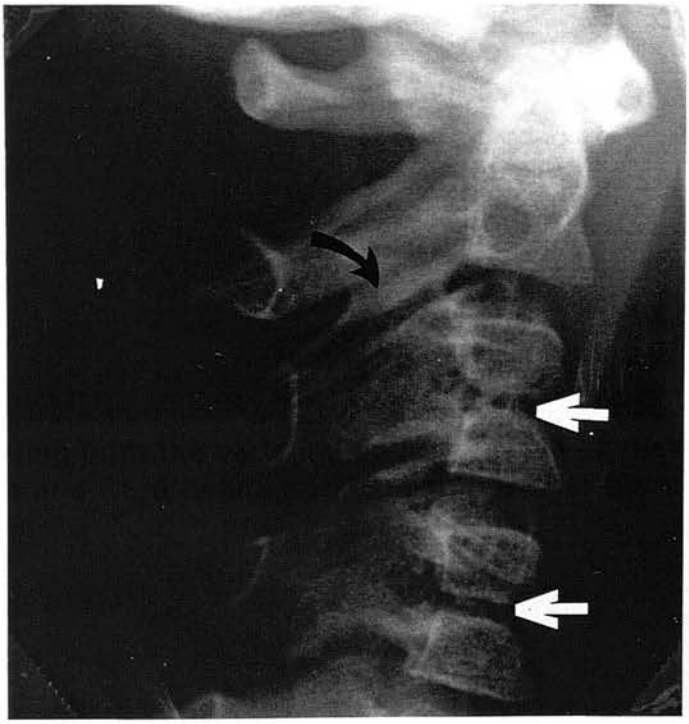


12, 13 No fusions

FIGURE 3.1 LEFT LATERAL CERVICAL SPINE RADIOGRAPH OF CASE 12, AGE THREE MONTHS.

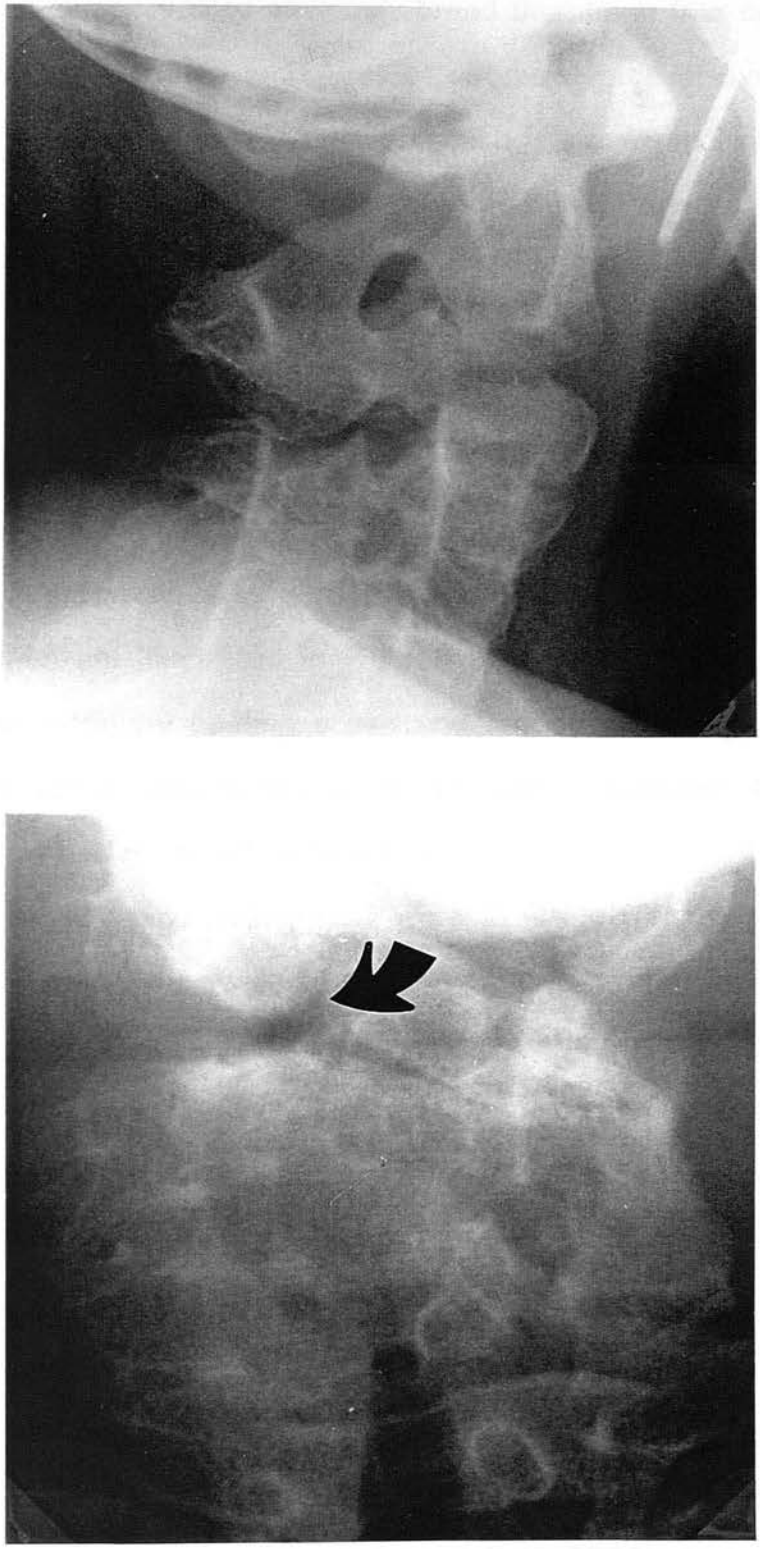
Radiographically normal.

FIGURE 3.2 RIGHT LATERAL RADIOGRAPH OF THE SAME CASE AT AGE SIX YEARS



Fusions affecting both the vertebral bodies and the posterior elements at levels C3/4 and C5/6 (white arrows) and posterior elements C2/C3 (black arrows).

FIGURE 3.3 RIGHT LATERAL AND ANTERO-POSTERIOR RADIOGRAPHS OF CASE 1 AGE SEVEN YEARS



Note the block fusion affecting all levels, and "Butterfly" vertebra C3 (arrowed).

THE HANDS

Clinical examination revealed obviously broad thumbs in four cases, an example of which is shown in Figure 3.4. Some degree of syndactyly was seen in 3/21 cases, an example of which is shown in Figure 3.5. Two cases (no's 12 and 25) required surgery to release bilateral complete syndactylies affecting the 3rd web space and bilateral incomplete syndactylies affecting the second web spaces.

The more severe combination of anomalies of shortening, radial deviation greater than 15 degrees of the index finger and short thumbs resulted in functional deficit in four cases (no's 7,11,12 and 16), such that surgical intervention was recommended to correct the deformity. These anomalies are illustrated in Figures 3.6 and 3.7. The principal complaint was difficulty holding a pen and writing, and this was not apparent until school age in any of these cases. However, the little finger anomalies had no affect on function.

A total of twenty nine radiographs were available from twenty one cases. Four cases were considered to be normal (case no's 2,8,13 and 18). Serial studies were available for six cases (no's 3,10,12,15,16 and 21). Of these only case 12 showed any evidence of progressive fusion, and this involved a single site with fusion between the phalanges of the thumbs.

The findings included both soft tissue and a wide range of skeletal anomalies, with the thumbs, fingers, metacarpals and carpals all demonstrating anomalies on occasion. There were also some differences between chronological age and bone age as measured against radiographic normals (Greulich and Pyle 1959), but no clear

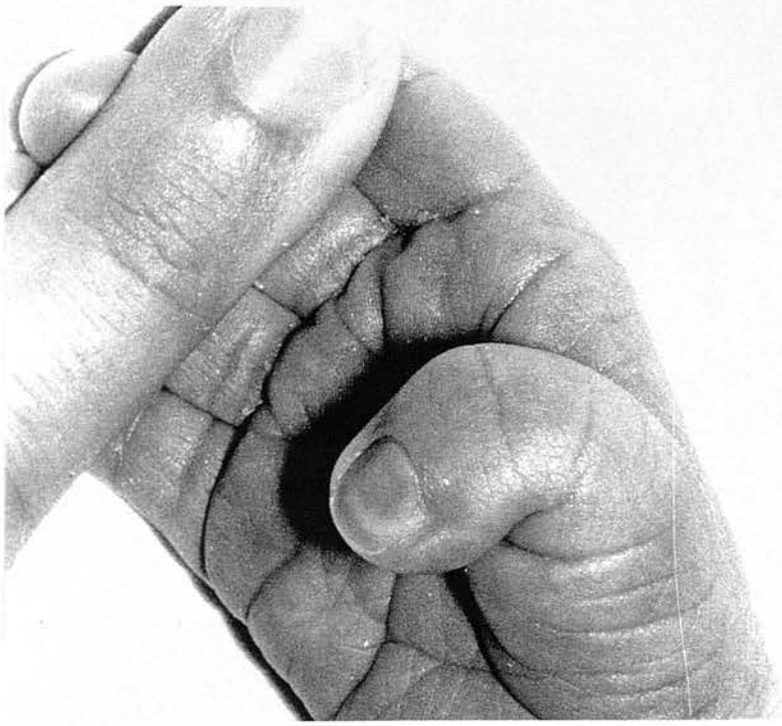
pattern emerged. The types and incidence of anomalies is shown in Table 3.6.

The most common anomalies were either hypoplasia (or rarely absence) of the middle phalanx of the little and index fingers. More than half the cases demonstrated either of these anomalies with many examples co-existing. This finding was in marked contrast to radiographically broad thumb phalanges which are associated with the finding of broad thumbs. Broad thumbs are considered to be classical features of Pfeiffer syndrome yet were only obvious in 4/21 cases. Since all these cases had been diagnosed as Pfeiffer syndrome on the basis of their phenotypic appearance, this apparent discrepancy requires explanation. One possibility could be that broad thumbs seen clinically may not necessarily be associated with radiologically broad phalanges, the thickened soft tissue accounting for the difference. Further studies comparing the clinical and radiological appearances will clarify this.

TABLE 3.6 SKELETAL ANOMALIES OF THE HANDS.
21 cases, 4 completely normal. None asymmetrical.

Anomalies		No. of Cases
DIGITAL ANOMALIES		
Thumb	Terminal phalanx broad	4
Thumb	Proximal phalanx broad	4
Thumb	Proximal phalanx "angel wing epiphysis"	3
Index	Terminal phalanx hypoplastic	4
Index	Terminal phalanx curved epiphysis	1
Index	Terminal phalanx radial deviation	3
Index	Middle phalanx hypoplastic	7
Index	Middle phalanx absent	2
Middle	Terminal phalanx hypoplastic	3
Middle	Middle phalanx hypoplastic	1
Middle	Proximal phalanx pseudoepiphysis	1
Ring	Terminal phalanx hypoplastic	3
Ring	Terminal phalanx radial deviation	1
Ring	Middle phalanx hypoplastic	1
Little	Terminal phalanx hypoplastic	3
Little	Middle phalanx hypoplastic	13
Little	Middle phalanx absent	2
METACARPAL ANOMALIES		
Tapering		1
Fusion between 4th and 5th		2
Hypoplastic 4th metacarpal		1
Proximally positioned metacarpals		1
CARPAL ANOMALIES		
Small in relation to metacarpals		2
Fusion of Capitate with Hamate		2
BONE AGE (Greulich and Pyle, 1959)		
Increased		3
Normal		16
Decreased		4

FIGURE 3.4 PHOTOGRAPH OF THE RIGHT HAND OF CASE 23 AT AGE THREE MONTHS

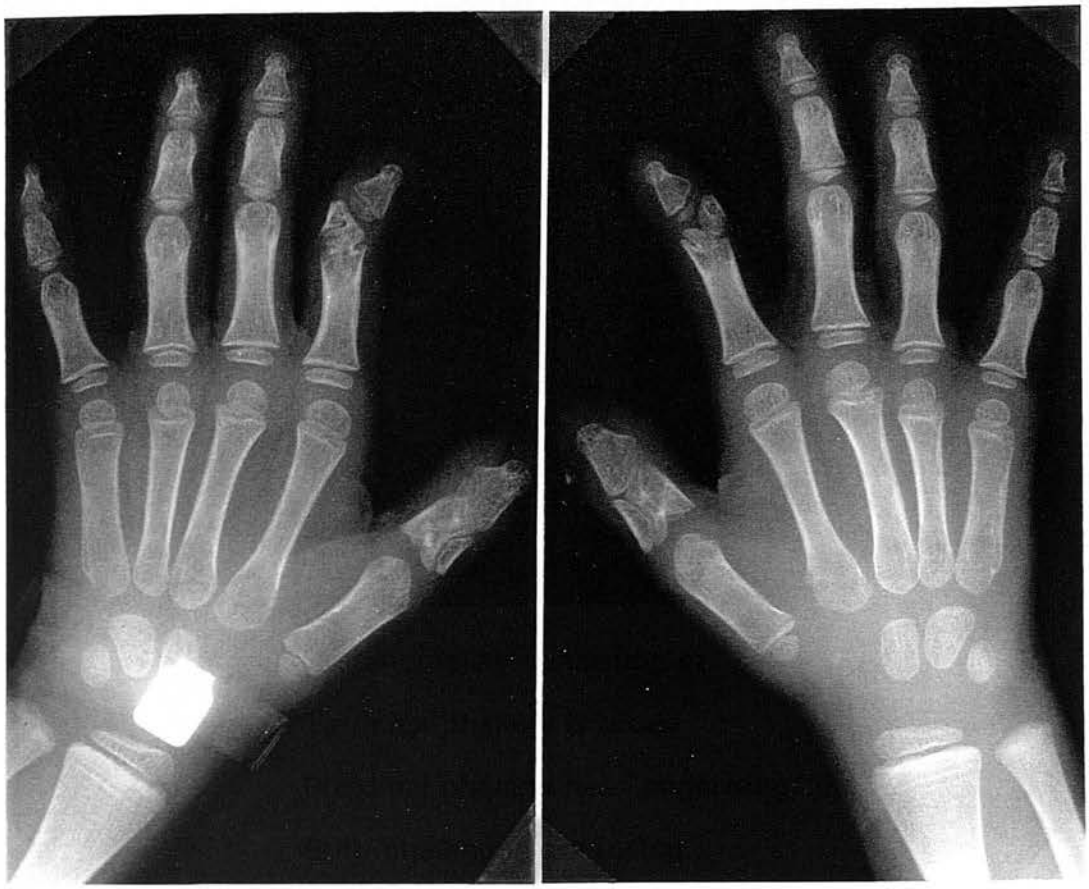


Note the "classical" finding of broad thumb in this syndrome.

FIGURE 3.5 PHOTOGRAPH OF BOTH HANDS OF CASE 12 AT AGE NINE MONTHS

Bilateral complete syndactyly of the 3rd web space and incomplete syndactyly of the 2nd web space.

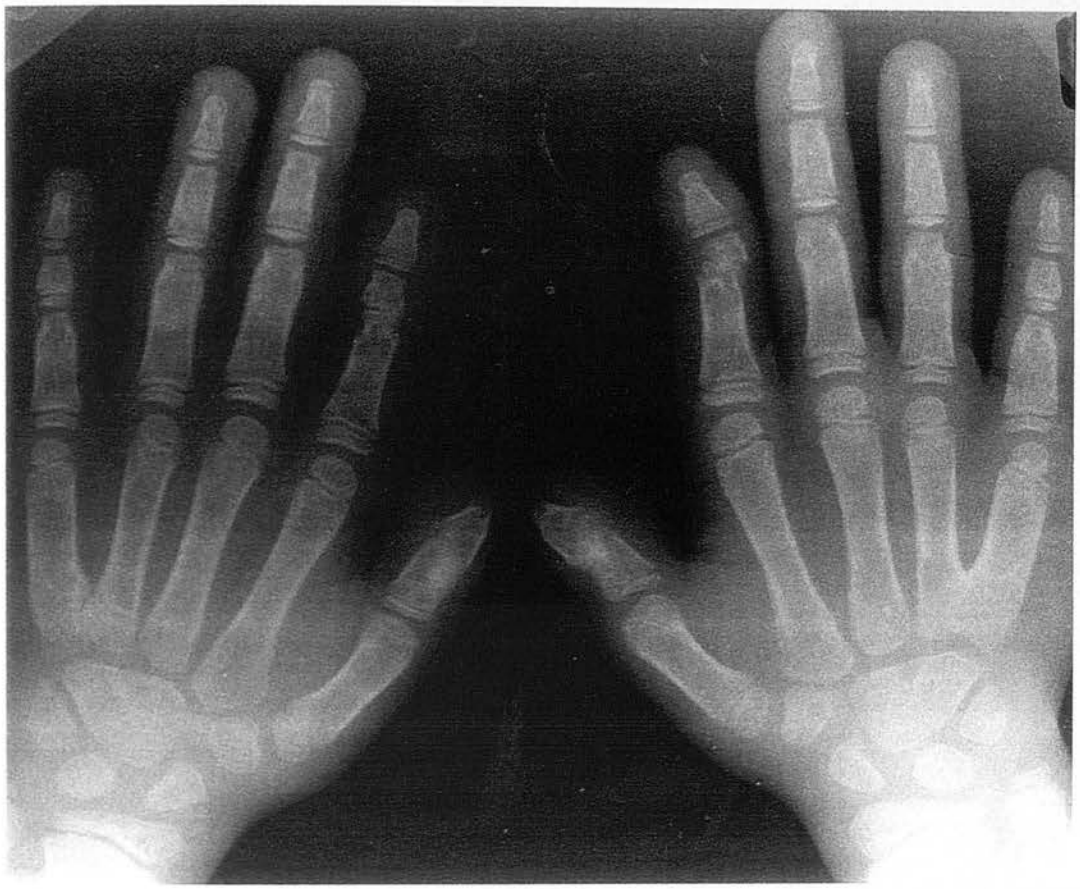
FIGURE 3.6 RADIOGRAPH OF BOTH HANDS OF CASE 12 AGE FIVE YEARS



Note the multiple digital anomalies consisting of:

Thumb:	Terminal phalanx is broad
	Proximal phalanx has "angelwing" epiphysis
	Both phalanges are fusing.
Index finger:	Terminal phalanx is both radially deviated and triangular
	Middle phalanx is hypoplastic
	Proximal phalanx is hypoplastic
	Proximal and Middle phalanges are fusing
Middle finger:	Terminal phalanx is triangular
Ring finger:	Terminal phalanx is triangular
Little finger:	Middle phalanx is hypoplastic

FIGURE 3.7 RADIOGRAPH OF BOTH HANDS OF CASE 16 AGE FOURTEEN YEARS



Note the multiple anomalies consisting of:

Thumb:	Both phalanges are fused
Index finger:	Middle phalanx is hypoplastic and radially deviated
	Terminal phalanx is radially deviated
Little finger:	Middle phalanx is hypoplastic
Metacarpals:	Fusion 4th and 5th proximally
Carpals:	Fusion of the Capitate and Hamate.

Bone age delayed by one year (Greulich and Pyle, 1959).

THE FEET

Clinical examination showed the presence of broad big toes in eleven cases. This deformity is a classical feature of the condition (Gorlin *et al.,* 1990) and an example is shown in Figure 3.8. Syndactyly was observed in two cases (no's 12 and 25), see Figure 3.9. All the web spaces were affected to some degree and both cases were symmetrical, see Figure 3.9.

Twenty seven radiographs from twenty two cases were obtained. Four cases (no's 4,10,11 and 24) had serial studies available. Three were deemed to be normal in all respects (case no's 5, 7 and 18).

A wide range of anomalies including altered bone morphology and fusions between bones were seen, the incidence and distribution of these are shown in Table 3.7. The range of abnormalities ranged from none to "Apert like" feet (case 16) which are shown in Figure 3.10.

The toes were the most common site for anomalies to occur. Hypoplasia of the middle phalanx in toes 2 - 5, was the most common anomaly seen occurring in 13/22 cases, an example is shown in Figure 3.11. The big toe was also frequently abnormal with both distal and proximal phalanges either abnormally broad or triangular shaped, and fusion between the two was common. The cases exhibiting fusion of the phalanges of the hallux (case no's 3,6,7,8,10,12,13,16,19 and 24) all occurred in patients older than four years. Only one case of the four undergoing serial studies showed evidence of progressive fusion (case 4) affecting the cuneforms.

The metatarsals and tarsals were only occasionally anomalous. The 1st metatarsal was the most often affected, exhibiting anomalies which included abnormal width, transverse fusion proximally, and a single case

of complete duplication (case 7). The tarsals exhibited cuneform fusion or calcaneo-cuboid fusion only, with a single exception (case 16), who had multiple fusions but with sparing of the talo-navicular joint. The sparing of the talo-navicular joint was similar to that seen in cases of Apert syndrome, (see Chapter Four). Those cases with fusions of the tarsals and metatarsals were all aged over six years of age.

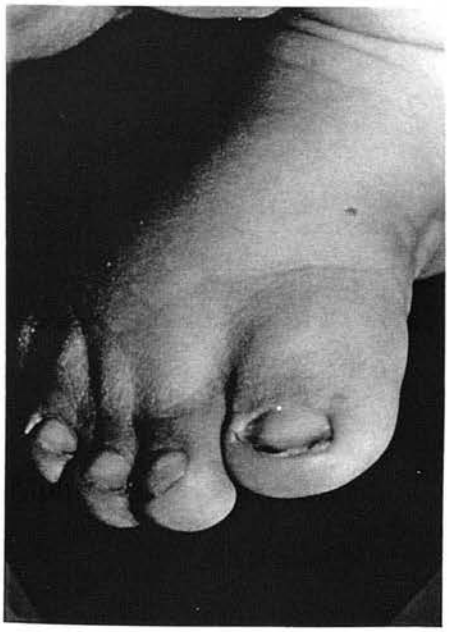
TABLE 3.7 ANOMALIES OF THE FEET IN PFEIFFER SYNDROME.
Cases 22, 3 cases normal. None asymmetrical.

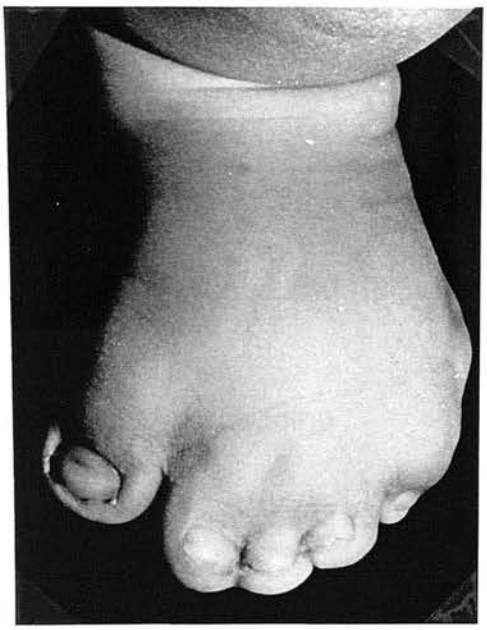
Anomaly	No. of cases
HALLUX	
Distal phalanx triangular	5
Distal phalanx broad	12
Distal phalanx medially displaced	3
Proximal phalanx triangular	4
Proximal phalanx broad	9
Proximal phalanx "angelwing epiphysis"	3
Proximal phalanx laterally displaced	2
Fusion distal and proximal phalanges	10
TOES 2-5	
Distal phalanx hypoplastic	10
Middle phalanx hypoplastic	13
Middle phalanx absent ossification	3
Proximal phalanx hypoplastic	1
Fusion middle and distal phalanges	3
METATARSALS	
1st Metatarsal broad	4
1st Metatarsal proximal duplication	1
1st Metatarsal complete duplication	1
1st Metatarsal pseudoepiphysis	1
2nd Metatarsal pseudoepiphysis	1
2nd Metatarsal hypoplastic	1
3rd Metatarsal hypoplastic	1
Transverse fusions	3
TARSALS	
Bifid Cuneforms	2
Fusion of cuneforms	3
Calcaneo-cuboid fusion	2
Multiple fusions (with talo-navicular sparing)	3

FIGURE 3.8 PHOTOGRAPH OF THE RIGHT FOOT OF CASE 23 AT AGE THREE MONTHS

"Classical" finding of broad big toe in this syndrome.

FIGURE 3.9 PHOTOGRAPH OF BOTH FEET OF CASE 12 AGE NINE MONTHS





Multiple web syndactylies

FIGURE 3.10 RADIOGRAPH OF BOTH FEET OF CASE 16 AGE FOURTEEN YEARS

Note the multiple "Apert like" anomalies.

Hallux:	Distal and proximal phalanges both broad and fusing together
Toes 2-5:	Middle phalanges hypoplastic and undergoing symphalangism.
Metatarsals:	1st proximal duplication Transverse fusion between 1st and 2nd metatarsals
Tarsals:	Multiple fusions with sparing of the talo-navicular and 5th metatarsal-cuboid joints

FIGURE 3.11 RADIOGRAPH OF THE RIGHT FOOT OF CASE 11 AGE ELEVEN YEARS

Note the following digital anomalies:

Hallux: Broad phalanges with duplication of the proximal phalanx.

Toes 2-5: Hypoplastic middle phalanges (arrowed)

THE ELBOWS

Clinical examination of the elbows was performed in twenty one cases and revealed a reduced range of motion in seven cases. A reduction in flexion/extension was noted in these seven cases, with a further five cases demonstating reduction in pronation/suppination. These five cases all had fixed flexion deformity of the elbow greater than 10 degrees (case no's 2,10,13,14 and 19), an example of which is shown in Figure 3.12.

Radiographs of the elbows were available for sixteen cases. Five cases (no's 6,18,21,22 and 25) were normal, but a wide range of anomalies were seen in the other eleven cases. These are shown in Table 3.8. Three cases exhibited asymmetrical anomalies, with right and left sides recorded separately.

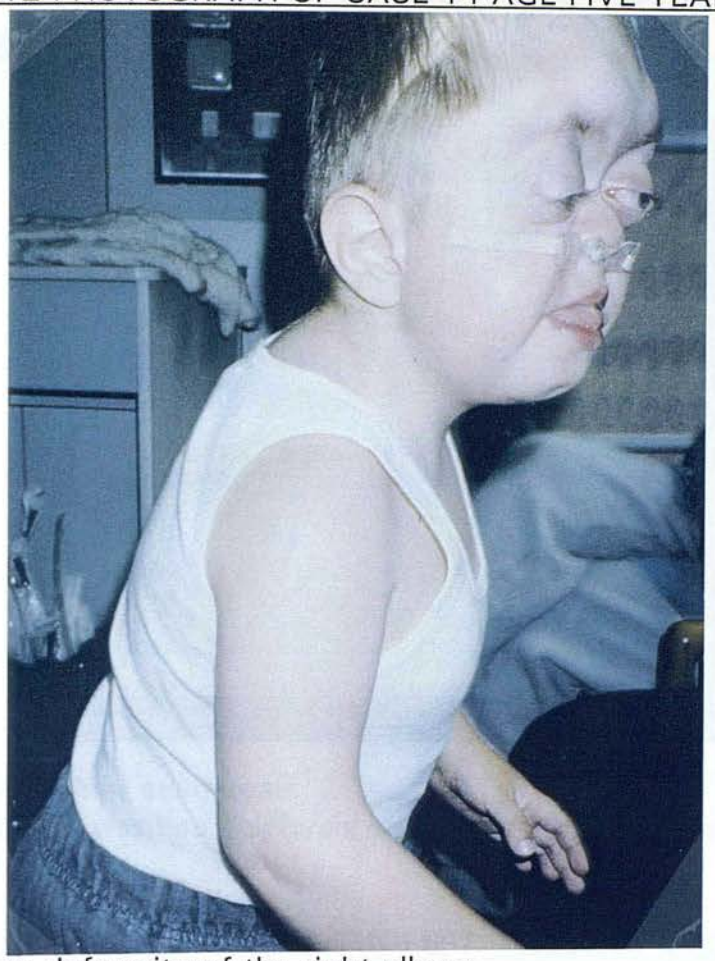
The ages of cases with radiographic anomalies ranged from just two months of age (case 4, which is shown in Figure 3.15), to the skeletally mature (case 8), aged seventeen years. The radial head epiphysis was the most common site for anomalies with examples of absence, late appearance and early fusion all seen, in half of the cases studied. The radio-ulnar and humero-ulnar joints were commonly subluxed or dislocated, and more rarely exhibited synostosis; an example is shown in Figure 3.14. Case 14 exhibited complete elbow synostosis and is shown in Figure 3.13.

Serial studies were available in three cases (no's 15,19 and 21). Progressive fusion was seen in case 15, and for case 19 although no fusions were present the humero-ulnar joint space was reduced in size suggesting possible late fusion. Case 21 was only one year old at the time of the last radiograph.

TABLE 3.8 ELBOW ANOMALIES IN PFEIFFER SYNDROME.
16 cases, 5 normal

Anomaly	No. of cases
Asymmetrical anomalies	3
A. BONE ANOMALIES	
HUMERUS	
Anterior notch	1
Absent external epicondyle	2
Absent epiphyses	2
OLECRANON	
Elongated with deep fossa	2
Absent epiphyses	2
Epiphyseal delay	1
RADIUS	
Radial head epiphyseal delay	1
Radial head epiphyses absent	7
Radial head premature epiphyseal closure	1
Radial head "mushrooming"	2
B. JOINT ANOMALIES	
Complete synostosis	1
Humero-ulnar joint space reduced	2
Humero-ulnar synostosis	3
Humero-ulnar dislocation	3
Radial head subluxation	3
Radial head dislocation	5
Radio-ulnar synostosis	2

FIGURE 3.12 PHOTOGRAPH OF CASE 14 AGE FIVE YEARS



Fixed flexion deformity of the right elbow

FIGURE 3.13 ANTERO-POSTERIOR VIEW RIGHT ELBOW OF CASE 14 AGE FIVE YEARS.

Complete synostosis

FIGURE 3.14 LATERAL RADIOGRAPH OF THE RIGHT ELBOW OF CASE 2 AGE SIX YEARS

Early humero-ulnar synostosis
Radial head has ossified epiphysis with "mushrooming", and is dislocated

FIGURE 3.15 RADIOGRAPH OF THE LEFT ELBOW OF CASE 15 AGE TWO MONTHS

Humerus abnormal distal morphology with anterior notch (arrowed)
Olecranon is elongated with a deep notch and producing an abnormal joint space with the humerus
Radial head is enlarged

THE SHOULDERS

Clinical examination of the shoulders was performed in twenty one cases. The most striking feature was the "squared off" appearance of the shoulders, an example of which is shown in Figure 3.16. There was a reduced range of movement in five cases (no's 2,11,12,13 and 14). Abduction was reduced in all these cases by more than 10 degrees. The most severe case (no. 14) could only abduct to 60 degrees. Three of these cases had reduction of both external/internal rotation and flexion/extension. All movements were symmetrical.

The results of radiological examination of the shoulders were available for seventeen cases. One radiograph was discarded as the quality was deemed too poor to make an assessment, leaving sixteen cases. Serial studies were available in three cases (no's 2, 19 and 15). The age of the cases at the time of the radiograph ranged from two months to fourteen years, with a median age of four years.

Five cases were normal (case no's 6,13,18,22 and 25), whilst the remainder showed several different anomalies which ranged in their severity between the cases. No cases of fusion were seen. All cases were symmetrically affected. The anomalies identified are shown in Table 3.9.

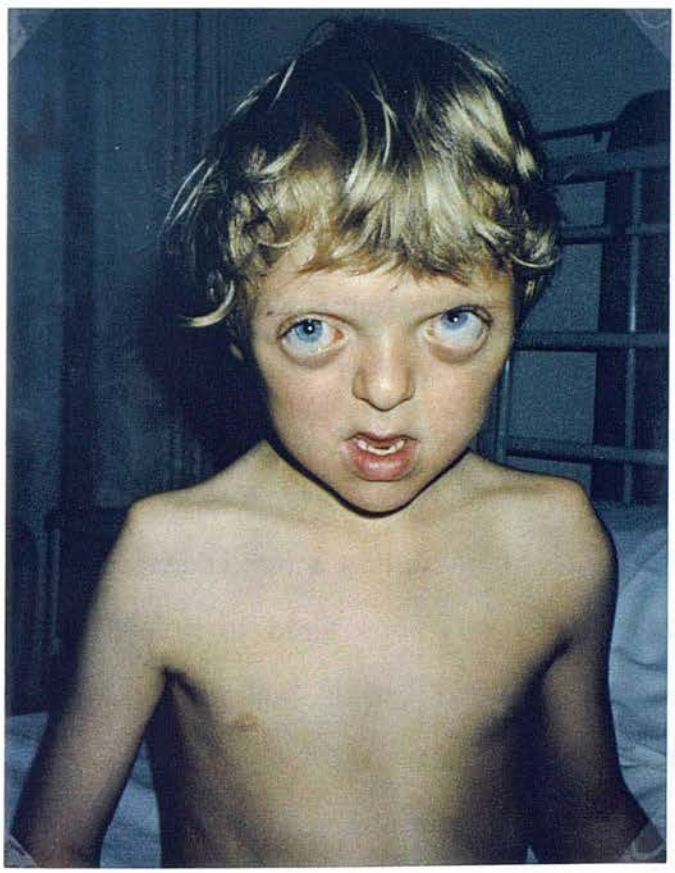
The common anomalies were the presence of a large acromium (an example is shown in Figure 3.17), and flattening or delay of the upper humeral epiphysis, with more than half of the cases having either or both of these anomalies present.

TABLE 3.9. ANOMALIES OF THE SHOULDERS IN PFEIFFER SYNDROME.

16 cases, 5 normal. None asymmetrical.

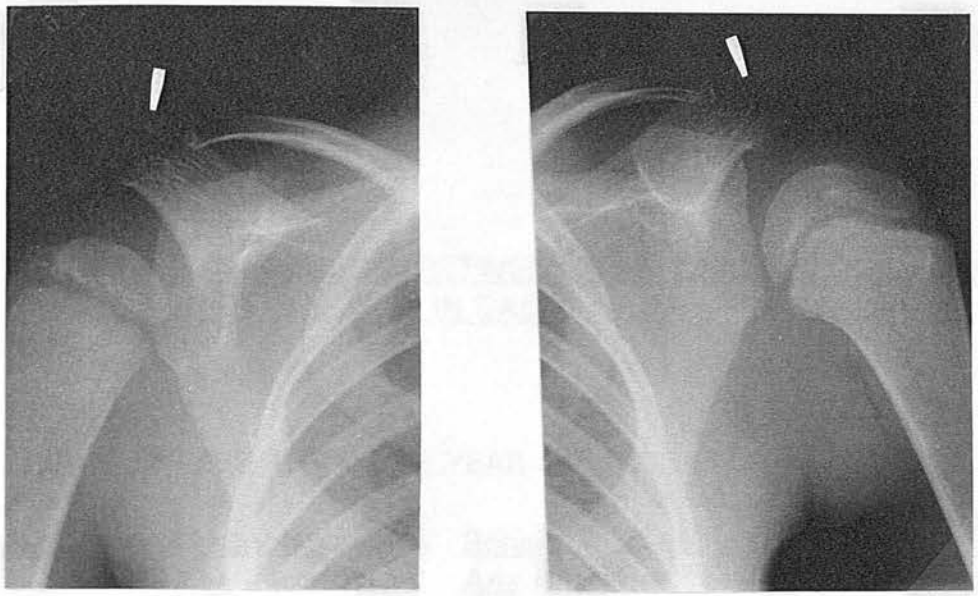
Anomalies	No. of Cases
A. BONE ANOMALIES	
Acromium enlarged	8
Lateral clavicular hooks	2
Upper humeral epiphysis flattened	4
Upper humeral epiphysis delayed	4
B. JOINT ANOMALIES	
Glenoid fosse absent	4
Glenoid fosse hypoplastic	1
Reduced joint space	1

FIGURE 3.16. PHOTOGRAPH OF CASE 6 AGE SIX YEARS



Note the "squared off" shoulders.

FIGURE 3.17 ANTERO-POSTERIOR RADIOGRAPH OF THE SHOULDERS OF CASES 6 AGE SIX YEARS



Note the enlarged acromium processes (arrowed) and absent glenoid fosse

THE KNEES

Clinical examination of the knees, in all cases, was unremarkable.

Radiological examination of the knees was undertaken in seven cases, and a serial study was performed in case 15. Apart from cases 7 and 14, these examinations were performed in children below one year of age as part of a skeletal survey. All seven cases demonstrated anomalies of the upper tibial epiphysis which was small and flattened, an example is shown in Figure 3.18.

The knee radiographs were compared to standardised normals as a method of assessing of bone age. This is more accurate than using hands in infants (Pyle and Hoerr, 1969). All cases below one year showed delay in bone age, the results are shown in Table 3.10. The single serial study, case 15, confirmed the retarded development both at 3 months and ten months. Curiously, the two studies available in

cases older than one year old, showed an increased bone age in relation to their chronological age.

TABLE 3.10 COMPARISON BETWEEN THE CHRONOLOGICAL AGE AND BONE AGE OF THE KNEE IN CASES OF PFEIFFER SYNDROME
7 cases

CASES AGED LESS THAN ONE YEAR

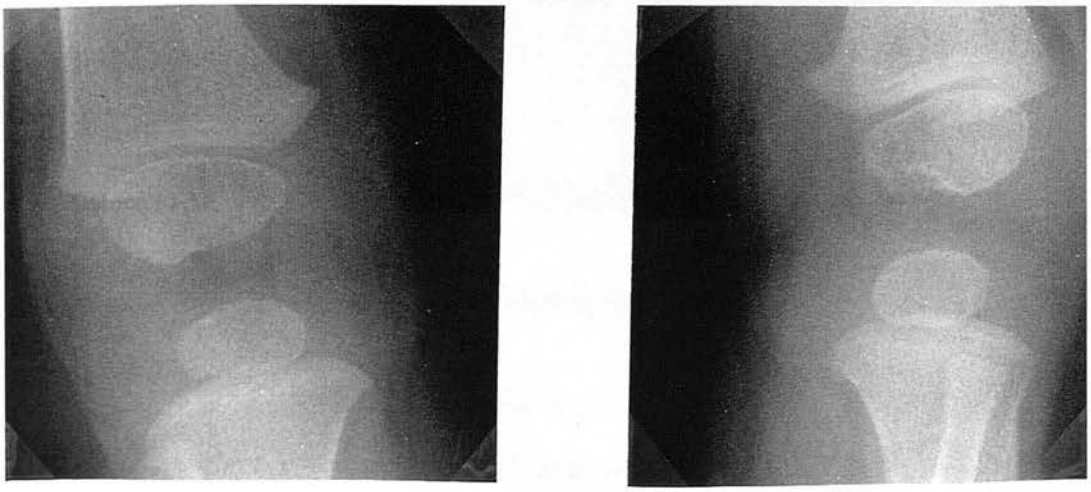
Case number	Chronological Age (Months)	Bone Age (Months)	Delay (Months)
4	10	7	3
15	3	1	2
	10	2	8
19	2	7/12i.u.	4
21	8	8/12i.u.	9
25	3	7/12i.u.	5

i.u. = interuterine age

OLDER CHILDREN

Case Number	Chronological Age(Years)	Bone Age (Years)	Increase (Years)
7	7	8	1
14	5	6	1

FIGURE 3.18 ANTERO-POSTERIOR VIEW OF THE KNEES OF CASE 15 AT AGE TEN MONTHS



Small upper tibial epiphysis
Bone age 2 Months (Pyle and Hoerr, 1969)

THE WRISTS

Wrist examination was universally unremarkable. Radiographs of the wrist, rather than the hands were reviewed in five cases. Two cases with normal elbow fuction were noted to have abnormal widening of the distal radius. Two cases who had dislocation of the humero-ulnar joint were noted to have secondary deformity at the wrist consisting of shortening of the distal ulna.

OTHER SITES

Chest radiographs of nine cases were reviewed, but no rib anomalies were detected. No other sites were available.

GENETICS

All the mutations identified in this series affected the FGFR 2 gene and are shown in Table 3.11.

TABLE 3.11 THE MUTATIONS OF CASES OF PFEIFFER SYNDROME

Case No.	Mutation	Amino Acid Change
2.	T1036 to C	Cysteine 342 replaced by Arginine
3.	G1037 to A	Cysteine 342 replaced by Tyrosine
10.	T1036 to A	Cysteine 342 replaced by Arginine
13.	T1036 to C	Cysteine 342 replaced by Arginine
15.	T1036 to C	Cysteine 342 replaced by Arginine
16.	Splice site mutation at nucleotide 68 in exon 7	
19.	T1036 to C	Cysteine 342 replaced by Arginine
20.	G1037 to C	Cysteine 342 replaced by Serine

Cases 2,13,15 and 19 all have the same mutation T1036 to C transition. (Case 10 has a T1036 to A transition, although it results in the same amino acid substitution as cases 2,13,15 and 19).

Note. This phenomonen results because there are a larger number of possible combinations of three bases in a codon than the number of aminio acids; the first two bases are often most important in determining which amino acid is synthesized, while different third bases in the codon may code for the same amino acid. This phenomonen is called genetic "wobble".

DISCUSSION

A wide range of anomalies affecting the morphological appearances of the bones, epiphyses close to joints, and the presence fusions have been demonstrated at a number of sites. These findings extend the current understanding of broad thumbs and big toes being the extracranial manifestations of this condition (Gorlin *et al.,* 1990).

CLINICAL EXAMINATION

The unremarkable height and weight measurements are not unexpected given the almost complete absence of anomalies in previous reports. The only report of short stature was associated with a reduction in length of both the humerus and the femoral neck (Saldino *et al.,* 1972).

Few visceral anomalies were present in the cases studied. Previous reports have associated the condition with the following: pyloric stenosis, umbilical hernia, bifid scrotum (Asnes and Morehead, 1969; Cohen, 1986; Gorlin *et al.,* 1990), prune belly syndrome and midgut malrotation (Barone *et al.,* 1993). The cardiac and cardiovascular anomalies have not been reported previously, but association with anal anomaly has been noted before (Cohen, 1986; Ohashi *et al.,* 1993). In the cases studied the results do not support the proposal that gastro intestinal and abdominal wall anomalies are common features of Pfeiffer syndrome (Barone *et al.,* 1993).

CERVICAL SPINE

The presence of radiological abnormalities of the cervical spine was seen in 16 of the 23 cases (70%). This is considerably higher than the incidence in the normal population of 0.5 - 3% (Shands and Bundens, 1956; Gray *et al.,* 1964).

The incidence of fusions is similar to that reported in other series: 7/11 cases (Moore *et al.,* 1995), 3/7 cases (Hemmer *et al.,* 1987), 2/3 cases (Saldino *et al.,* 1972) and 1/3 cases by (Cohen, 1993a). The slightly higher incidence of fusions in this series, 16/23 cases, may be due to the progressive nature of cervical fusions in this condition. The median age at the time of the last available radiograph was seven years, whereas the median age in the next largest study by Moore *et al.,* (1995) was just three months. There is strong radiological evidence from the results of those who underwent sequential studies, of progressive vertebral fusion.

The pattern of fusion within the cervical spine is itself interesting. While fusions occur at all levels, C2/C3 is the most common level for fusions of both the vertebral body and the posterior elements. This level is also the most commonly affected level in the normal population (Brown *et al.,* 1964). This result is similar to the findings of all of the previous studies (Saldino *et al.,* 1972; Hemmer *et al.,* 1987; Cohen, 1993a; Moore *et al.,* 1995). Detailed examination of the sites of fusion in sequential studies revealed a curious pattern. Fusion was observed to occur in the posterior elements prior to body fusion at the C2/C3 level, and in four cases the last radiograph showed fusion of the posterior elements only at this level. By comparison, at the C5/C6 level, body

fusion preceded fusion of the posterior elements and one case had fusion of the body only.

The finding of block vertebrae in 8/23 cases suggests that this is not an uncommon development in this syndrome. This finding combined with the high incidence of fusions suggests that the cervical spine is particularly prone to the fusion process.

No previous reports of hypoplasia of the neural arches occurring in Pfeiffer syndrome could be found in the literature. "Butterfly" vertebra has not been recorded in Pfeiffer syndrome, although its occurrence in Crouzon syndrome has previously been reported (Hemmer *et al.,* 1987). The observation of hemivertebrae are also a new finding in Pfeiffer syndrome.

In this study five cases (no's 1,4,14,15, and 21) had clinically severe craniofacial manifestations of the syndrome with a cloverleaf skull (type 2 Pfeiffer; Cohen, 1993a). Case 21 was unusual in that there was a radiologically normal cervical spine on two separate examinations. This contasts to an earlier study (Moore *et al.,* 1995) where all of the four cases with the cloverleaf deformity in that study had abnormal radiographs, most exhibiting the more severe block fusions (Moore *et al.,* 1995).

The clinical consequences of all these cervical spine anomalies remains unclear as no direct adverse effects are recorded in the records of this series or any of the previously published reports. However, there is a risk of developing excessive movement in the joints either side of the fusions, so there is a potential risk with anaesthesia where the neck may be extended. This may be accentuated in block vertebrae, which have been shown to be not uncommon in Pfeiffer syndrome. Due to the

progressive nature of the fusions it would be prudent to obtain current cervical spine radiographs prior to anaesthesia for all those with Pfeiffer syndrome.

THE HANDS

Pfeiffer syndrome has been widely reported to have broad thumbs as part of the typical phenotypic appearance (Pfeiffer, 1964; Gorlin *et al.,* 1990; Cohen, 1993a). The results of this study revealed that obviously broad thumbs were not a common clinical finding in this series of cases with radiological evidence of broad thumb phalanges seen in just 4/21 cases. However, this contrasts to the finding of an unexpectedly much wider range of anomalies within the hands. There were anomalies demonstrated both in the soft tissues, producing syndactyly but also throughout the skeleton with phalanges, metacarpals and carpals affected, usually by fusions. However, 4/21 cases have shown that, on occasion, the hands can be, radiologically, entirely normal.

The low incidence of syndactyly in this series suggests that this is an uncommon finding. However, when it did occur the underlying skeleton was always abnormal, so this is an important clinical sign. The two cases of syndactyly both had symmetrical involvement of the hands and feet.

The frequency with which anomalies of the skeleton occurred at sites other than the thumbs was surprising given that they have been occasionally mentioned, although previous reports have given little prominence to these (Pfeiffer; 1969, Martsolf *et al.,* 1971; Saldino *et al.,* 1972; Escobar and Bixler, 1977; Cohen, 1993a). However, many of the earlier reports are based on case reports and smaller series than this

one, so the significance of these anomalies may have now become apparent with their observation in a relatively large number of unrelated cases.

It has been reported that Pfeiffer syndrome has an altered metacarpophalangeal pattern profile in comparison with normal data (Escobar and Bixler, 1977). Although their findings were obtained from only six cases it suggested that the anomalies resulting from mutation expression were both subtle and widespread.

The most common anomaly was hypoplasia or absence of the middle phalanx of the little and index fingers. These were demonstrated in 15/21 and 9/21 cases respectively. This contrasts to the finding of broad thumb phalanges, in just 4/21 cases (see Table 3.6).

The cases with radiographically normal hands are an interesting sub-group. Two cases with the same genetic mutation had severe craniofacial manifestations such that they required elective tracheostomy. However, the other 2 were siblings (cases 18 and 22) and had much milder craniofacial and other extracranial manifestations of the condition.

The clinical significance of these results to the affected individuals were in most cases minimal. However, surgical intervention was required in cases no's 7, 12 and 16 to improve function. Additionally, case 11 was offered surgery but declined. The surgery undertaken included syndactyly release and re-aligning osteotomies of the thumbs and index finger to improve "pinch grip" with a view to improving writing skills.

However, there are important clinical applications of these results for clinicians who have to diagnose patients on clinical grounds alone. The

clinical assessment of the thumbs to diagnose the condition can be unreliable, and even the radiographic features of the hands can be within the normal range.

THE FEET

The anomalies identified included both soft tissue and skeletal anomalies. The two cases of syndactyly were symmetrical, and the hands were also affected, although fewer web spaces were affected. The radiological anomalies in these twenty two cases ranged from none to multiple fusions, symphalangism and morphological changes producing "Apert like" anomalies of case 16. The feet produced the most variable manifestations of any site studied of the Pfeiffer syndrome patients. Case 16 reported difficulty with obtaining footwear, but no other clinical consequences were recorded in this population. No cases underwent surgery for the enlarged big toes, which has been previously described (Kissel *et al.,* 1992).

The majority of the anomalies occurred in the phalanges, although the metatarsals and the tarsals were on occasion affected. The finding of increased width of the distal and proximal phalanges of the hallux (12/22 cases and 9/22 cases respectively), is in keeping with the recognition that this is a cardinal feature of the syndrome (Gorlin *et al.,* 1990; Cohen, 1993a). This finding is in contrast to the findings in the hand where broad thumb phalanges were uncommon. However, the frequent finding of hypoplasia affecting the middle and distal phalanges has not been previously reported.

Fusions were found throughout the bones of the feet and often associated with dysmorphic bones, particularly the phalangeal bones of

the hallux. In the four cases in which serial studies were available, only a single case (case 4) demonstrated progression of fusion. This is perhaps because fusions are not progressive or are themselves a slow process or rare events. This last possibility seems unlikely given that a total of 8/22 cases had radiological evidence of fusion at one or more sites.

It is noteworthy that case 16 which demonstrated almost complete fusion of the tarsal bones had sparing of the talo-navicular joint. Indeed the radiological appearance so closely resembles an Apert foot (see Chapter Four), that the diagnosis might be questioned on this finding alone. However the diagnosis has been supported by the results of D.N.A. analysis.

There were four normal cases (cases 5, 7, 18 and 22) all of whom are teenagers and so are unlikely to subsequently develop fusions.

THE ELBOWS

Anomalies of the skeletal morphology and fusion have been shown to commonly occur around the elbow in Pfeiffer syndrome, with a variable range of severity. Previously, it has been stated that elbow anomalies only occur occasionally (Cohen, 1986; Gorlin *et al.,* 1990). These case reports have highlighted hypoplasia of the radial head and flattening of the humeral epicondyles (Saldino *et al.,* 1972). However, the suggestion that these are rare has been questioned more recently when it was found that elbow ankylosis can occur in all Pfeiffer syndrome subtypes, although with different frequencies (Cohen, 1993a). The results of this study with 11/16 cases who underwent radiological

examination exhibiting anomalies, supports the finding that anomalies of the elbows are common in Pfeiffer syndrome.

There is direct but tentative evidence from 2/3 serial studies that the fusions are progressive. These numbers are small and larger numbers of serial studies will be required to verify this. The epiphyses, particularly the radial head epiphysis, are commonly affected in the elbow. The abnormal epiphyses may produce changes in the morphology which then produce secondary deformity. The "mushrooming" of the radial head and joint subluxation or dislocation may be associated in this manner. This complicates the interpretation of the resulting anomaly at the elbow. The total deformity produced at the elbow may result directly by the action of the underlying mutation but may also include the result of secondary effects. However, it is noteworthy that some deformities were seen at two months of age long before the epiphyses were present. This suggests that it is not just the epiphyses which are important sites of primary FGFR expression.

THE SHOULDERS

The results show that the shoulders were commonly affected with 11/16 cases having radiological anomalies. The range and severity was much less than those anomalies of the elbow. Unlike other sites studied there was no evidence of fusion of the joint. The upper humeral epiphysis was noted to be commonly abnormal, suggesting that this epiphysis too is an important site for expression of the mutant gene.

Previous reports have described single cases of hypoplasia of the humeral head and an enlarged acromium (Saldino *et al.,* 1972) but

others have not mentioned radiographic anomalies of the shoulders (Martsolf *et al.,* 1971; Cohen, 1986; Gorlin *et al.,* 1990). The reason for so few reports, when anomalies have been commonly found in this population is unclear, but may be due to the subtlety of the signs in some cases.

Reduced function was discernable in five cases, but only apparent to the individual or their families in three cases. The absence of fusions, particularly progressive fusions, may indicate that function will be satisfactory. However, the long term affects of the abnormal shaped joint is not clear and studies of these in adult life will be necessary to determine whether there is an increased risk of degenerative disease in the anomalous joints.

THE KNEES

The finding of anomalies in the knee were unexpected. No previous reports of radiological anomalies of the knee could be found (Gorlin *et al.,* 1990; Cohen, 1993a; Taybi and Lachman, 1996). Where radiological examination was performed this had been reported as normal (Saldino *et al.,* 1972). The identification of anomalies of an epiphysis, given that they have been affected in many other joints, perhaps makes these findings not so suprising.

The finding of decreased bone age in all cases below one year is interesting and is in contrast to the results of radiological examination of the knees in Crouzon syndrome. These differences may be of use in assisting in the differential diagnosis of an atypical phenotype. The significance of increased bone age of the two older cases is unclear and further investigations will be required to confirm this.

OTHER VIEWS

The absence of rib anomalies is in contrast to an earlier study where hypoplasia of the twelth rib was demonstrated in a single case (Saldino *et al.,* 1972). These results along with the absence of other reports suggest that this may just have been an isolated finding. No pelvic radiographs were available so the previously reported small illiac angle (Martsolf *et al.,* 1971) could not be confirmed.

GENETICS

The genotypes in this series all result from mutations of the type 2 fibroblastic growth factor receptors, although the phenotype can also result from type 1 fibroblastic growth factor receptors (Muenke *et al.,* 1994).

These results suggest that there may be differences in the Pfeiffer phenotype depending on the type 2 fiboblastic growth factor receptor genotype, as shown in the differences in severity of craniofacial and extracranial manifestations of cases 2, 13 ,15, 19, and, case 16. This requires cautious interpretation as the numbers are small with case 16 being just a single case.

The results also show that marked differences in the phenotypes can exist for the same genotype, as highlighted by the shoulders in cases 2, 13, 15 and 19. These four cases all have severe craniofacial manifestations of the syndrome (case 15 has the cloverleaf deformity). They have all required cranial vault surgery for severe craniosynostosis within six months of birth, required the insertion of ventriculo-peritoneal

shunts for hydrocephalus and had difficulties with maintaining an adequate upper airway necessitating either facial advancement surgery at one year of age or continuous positive airway pressure (C.P.A.P.) therapy. The hands of cases 2 and 13 are normal, while cases 15 and 19 have mild manifestations of hypoplastic phalanges of the little and index fingers. This contrasts to the feet where they all have hypoplastic middle and distal phalanges, with broad big toes and have digital and talus fusions, apart from case 15 (who is still only one year old). The elbows are similarly severely affected with cases 2 and 15 exhibiting fusions, and cases 13 and 19 exhibiting major epiphyseal anomalies. The shoulders give a mixed picture with cases 4 and 19 normal, but cases 2 and 15 exhibiting both abnormal glenoids, acromia and anomalous humeral epiphyses. The cervical spines of these four cases are all severely affected with fusions at multiple levels.

In summary, the Pfeiffer phenotype with these craniofacial anomalies only show mild hand anomalies but a moderate incidence of anomalies of the remaining extracranial skeleton.

It is interesting to note that a wide range of phenotypes have previously been reported for cases of Jackson-Weiss syndrome, which also results from mutations of the FGFR 2 gene (Jabs *et al.,* 1994).

Case 16 with the splice mutation is a particularly interesting phenotype. This case has the severest manifestations of the hands and the feet which have many features in common with "Apert" syndrome (Figures 3.7 and 3.10). The elbows have radio-ulnar synostosis and absent epiphyses, the shoulders have small flattened upper humeral epiphysis, while the cervical spine has a block fusion affecting C2/C3 and C3/4. Craniosynostosis and facial deformity are present but have

not yet required surgery by the age of fourteen years. In summary this case with only moderate craniofacial manifestations has the severest anomalies of the hands and feet.

The mutation affecting case 20 is interesting because the change in D.N.A. sequence, Cys342Ser, has also been identified in a phenotypical case of Crouzon syndrome (case 5, Chapter Two). This has been previously reported (Rutland *et al.,* 1995). This was a female aged five years, with the following radiological findings. Serial studies of the cervical spine revealed progressive fusions. Radiographs taken at three months of age show the cervical spine to have fusion of the posterior elements at C2/3; but by three years of age vertebral body and posterior elements had also fused at C6/7 level, and by five years the fusions included the vertebral bodies of C5/6. The hands demonstrated bilateral hypoplasia of the middle phalanx of the little finger, and fusion of the capitate and hamate. The elbows demonstrated a subluxed humero-ulnar joint with separation of the radius and ulna. The shoulders demonstrated flattening of the upper humeral epiphyses and hypoplasia of the glenoid fosse. The feet demonstrated a triangular proximal phalanx of the hallux, hypoplastic middle and distal phalanges of toes 2-5, with calcaneocubiod fusion. These show that her extracranial manifestations were consistent with her diagnosis of Pfeiffer syndrome rather than Crouzon syndrome. Interestingly, the Crouzon syndrome (case 5, chapter Two) with this mutation had both severe craniofacial manifestations with marked maxillary hypoplasia and a block fusion of the cervical vertebrae, which can be features of Pfeiffer syndrome. These cases demonstrate the possible overlap between the syndromes.

The relationship between phenotype and genotype will become clearer with the identification of more genotypes by D.N.A. testing and accurately recording the phenotypic findings.

CONCLUSIONS

The study of the extracranial sites to investigate evidence of extracranial manifestations of the condition has produced some new and unexpected findings. This is despite the previously expressed caution in attempting to extend the variability of expression in Pfeiffer syndrome (Cohen, 1995). The epiphyses are important sites of expression and demonstrate anomalies at many sites within the skeleton.

The relatively few visceral and soft tissue anomalies suggests that anomalies here are rare, and suggests that expression of the mutant gene, although present in these sites, does not produce detectable results.

For the cervical spine both the incidence and severity of fusions in this series are greater than in any of the other complex craniosynostosis syndromes, or than in previously published reports. The reasons for this may reflect difficulties in establishing the correct diagnosis on clinical grounds leading to mixed samples, and by the interpretation of the radiographs. The level most commonly affected is C2/C3, which confirms the findings of earlier studies. The results of this study suggests that these fusions are progressive during childhood. Additionally, the congenital deformities seen including: hypoplastia of the neural arch of C1, hemivertebra and "Butterfly" vertebra have not

been described in this condition and may be a guide to the development of subsequent fusion, remembering that the incidence of fusions is high in this syndrome.

The study of the hands has shown a wide range of anomalies with digits, metacarpals and carpals all affected on occasion by fusions. The few cases with radiologically broad thumb phalanges is surprising given that broad thumbs are a cardinal feature (Cohen, 1993a). This discrepancy has been considered previously and it was proposed that such cases may represent isolated cases of Jackson-Weiss syndrome (Cohen, 1995). The anomalies of the middle phalanges of the little and index finger have been shown to be very common in this condition. These anomalies can be particularly useful in assisting diagnosis, but rarely result in loss of function or deformity that requires surgical intervention.

The feet may show a remarkably wide range of morphological anomalies, varying from none to "Apert like" anomalies. All parts of the feet can be affected by fusions apart from the talo-navicular joint. These anomalies, except in the severest cases, do not cause difficulties with walking or obtaining footwear.

The shoulders commonly show morphological changes particularly affecting the acromium, as well anomalies of the upper humeral epiphysis. However, unlike other sites, fusions have not been demonstrated. The reason for this is unclear and could be due to later appearance in adults (although this has not been reported), or due to genuine sparing at this site due to a local factor or factors.

The knees, commonly in childhood, showed anomalies of the upper tibial epiphysis, including delay in bone age. It may be useful to apply

this clinically when trying to reach a diagnosis in atypical cases. However, no cases of fusion of the upper tibial and femoral epiphyses was seen, which has been recently reported (Krauspe, 1996).

Three conclusions can be drawn from the genetic evidence which advances the current understanding of this syndrome.

Firstly, it suggests that there may be phenotypic differences associated with different genotypes. It has been suggested that there may be phenotypic differences between the type 1 and the type 2 fibroblastic growth factor receptor mutation genotypes (Schell *et al.,* 1995), but the results of this study are based on different mutations of FGFR 2. The evidence from this small series is tentative and larger numbers will be required to establish this. However, it has already been proposed that three different clinical subtypes exist (Cohen, 1993a), and these findings support this concept, implying that subgroups may be related to genotypes.

Secondly, there is evidence within this series that there are phenotypic differences within the same genotype, the reason for this is unclear but is an important observation in attempting to understand the developmental process.

Thirdly, the results of detailed examination of those Pfeiffer syndrome genotypes which have also been identified in Crouzon phenotypes, suggests that the genotype produces either a distinct Crouzon or a Pfeiffer phenotype, rather than a hybrid phenotype exhibiting a combination of clinical features.

There is strong evidence to support the concept of progressive fusions throughout childhood from the results of the cervical spine studies, with evidence also of this in the hands, feet, elbows but not the shoulders or

the knees. However, the evidence from sites other than the cervical spine is less convincing, but this may be due to the shortage of serial radiographic studies. Examination of the hands, feet and elbows only showed evidence of progressive fusion in 1/6, 1/4 and 2/3 cases respectively where serial studies were available. The incidence of progressive fusion at these sites in this condition remains unclear, but further radiographic serial studies of the limbs will determine this.

Finally, the clinical significance for function of the limbs, with progressive fusions occurring in different joints at the same time is not clear. Significant loss of function was rare and only demonstrated in the hands of four cases in this population. However, there must be a chance that this will happen in the future. Currently, two cases have undergone surgery to the hands to improve function.

It could be that the Rheumatologist and the Orthopaedic surgeon will have an increasing role to play in the management of those with affected joints in this condition. As more affected children reach adulthood, thus becoming skeletally mature, the progressive nature of the fusions may be result in them being even more severely affected (Krauspe,1996).

CHAPTER FOUR

CHAPTER FOUR

APERT SYNDROME

A total of sixty two cases of Apert syndrome were identified from the database of the Craniofacial Centre at Great Ormond Street Hospital. Nineteen cases were excluded because they could not be seen during the period of the study. The remaining forty three cases had their diagnosis made on the phenotypic appearance following clinical examination (by the author). The features which were of particular importance included a broad head, facial hypoplasia and syndactyly of both the hands and feet. All of these patients were also examined by a Consultant geneticist who agreed with the diagnosis in each case. The results of D.N.A. analysis were available in fourteen of these cases.

The ages ranged from three months to twenty years (with a median of eight years). There were twenty two males and twenty one females. All cases were the results of new mutations.

All forty three patients who attended Great Ormond Street Hospital during the period March 1995 - April 1996 were interviewed along with their parents to review their medical history and to perform a clinical examination including height and weight measurements. The height and weight measurements were compared to normal values (Tanner *et al.*, 1966), and to birthweight. This was supplemented by a radiographic examination, and review of existing medical and radiological records. The cases were assigned a number and the results of all investigations recorded. This is shown in Table 4.1.

The cervical spine and hand radiographs of most of these cases had previously been extensively studied, and the results pooled with data

other U.K. Craniofacial Units (Thompson *et al.*, 1996, Slaney 1996). The results of those studies will be discussed but the investigations were not repeated.

RESULTS

CLINICAL EXAMINATION

The clinical examination revealed loss of movement in the elbows, shoulders and hips, which are reported in more detail later. There were no obvious differences in height or weight records when compared to age and sex standards for both girls and boys (Tanner *et al*, 1966). However, close inspection revealed that the four girls who were skeletally mature (cases 14, 20, 25 and 29) were in the lowest centiles. Their heights were all below the twenty-fifth centile and three of these cases were below the tenth centile. An example is shown in Figure 4.1.

The boys heights and weights both ranged from the twenty-fifth to the nintieth centile. The girls heights ranged from the third centile to the ninetieth centile and their weights from the twenty-fifth centile to the ninetieth centile.

Associated anomalies were few; case 1 had a ventricular septal defect, case 16 had talipes equinovarus and case 34 had congenital pyloric stenosis. Case 17 had a congenital gut malrotation and required laparotomy shortly after birth. All of the cases who were teenagers had widespread acne vulgaris, but only case 25 had involvement of the forearms.

FIGURE 4.1 PHOTOGRAPH OF CASE 14 AGE NINETEEN YEARS

Height 5 feet 1 inch (155 centimeters).

TABLE 4.1 THE CASES AND THEIR RADIOLOGICAL EXAMINATIONS

Case No.	Sex	Present Age (Years)	Elbows	Shoulders	Feet
1.	F	1	1	1	1
2.	F	4	1	1	-
3.	F	4	1	-	1
4.	M	13	1	1	1
5.	M	6/12	-	-	2
6.	M	5	1	1	2
7.	M	9	1	2	1
8.	M	5	1	1	3
9.	M	20	1	-	3
10.	M	14	1	1	-
11.	F	9	1	1	2
12.	F	13	1	1	1
13.	F	5	1	1	3
14.	F	19	-	1	2
15.	F	2	1	1	3
16.	F	3	1	-	2
17.	M	2	1	1	1
18.	F	9	1	-	1
19.	F	3	1	1	1
20.	F	16	1	1	1
21.	F	4	1	-	1
22.	F	5	2	1	-
23.	M	1	-	-	1
24.	M	2	1	1	2
25.	F	18	1	1	-
26.	F	3	1	1	1
27.	M	11	1	1	3
28.	M	10	2	2	4
29.	F	17	1	1	1
30.	M	1	-	-	1

Continued overleaf

TABLE 4.1 THE CASES AND THEIR RADIOLOGICAL EXAMINATIONS
(continued)

Case No.	Sex	Present Age (Years)	Elbows	Shoulders	Feet
31.	F	10	1	1	2
32.	M	12	-	1	1
33.	M	2	1	-	1
34.	M	11	1	1	2
35.	F	13	1	1	3
36.	M	5	1	-	1
37.	M	12	1	1	1
38.	M	8	-	-	1
39.	F	5	1	1	2
40.	F	7	-	-	2
41.	M	3/12	1	1	1
42.	F	3/12	1	1	1
43.	M	21	1	-	-
Total cases			36	30	38
Total films			38	32	63
Serial studies			2	2	17

THE CERVICAL SPINE

Thirty four of the cases in this study of Apert syndrome had previously had their cervical spine radiographs pooled with radiographs of children with Apert syndrome from two of the United Kingdom Supraregional Craniofacial centres, to study the cervical spine (Thompson *et al.,* 1996). The methods used were similar to those undertaken in the examination of the cervical spines in this study (Chapters Two, Three and Five). The findings of the study by Thompson *et al.*, (1996) will be considered and compared with the results obtained from this study of Crouzon, Pfeiffer and Saethre-Chotzen syndromes. Fifty nine cases were included in their study, eighteen cases had sequential radiological studies. Fusions were seen in 63% of cases but fusion was rare before twelve months of age. Progressive fusions were seen in 10/18 sequential studies. The level most commonly affected was C5/C6, and fusion of the vertebral bodies preceded fusion of the posterior elements at this level. Congenital anomalies were rare, the only type of anomaly seen was enlargement of the dens, which occurred in two cases.

THE HANDS

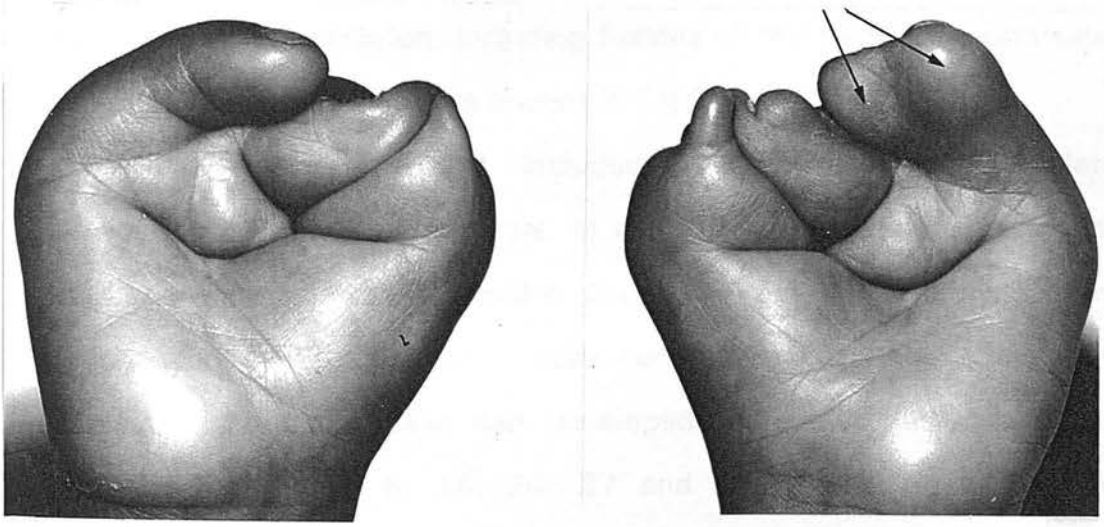
The radiographs of the hands of many of these cases have already been studied and the detailed results of these findings compiled by Dr S. F. Slaney (Slaney, 1996), and this was not repeated. Limited study of the hand radiographs was undertaken to review those cases with serial radiographic studies. All of the available cases demonstrated evidence of progressive fusions affecting the phalanges, metacarpals and carpals. However, transverse fusions of the phalanges was not

seen in any case where simple syndactyly release to separate the digits had been undertaken before two years of age.

Clinical examination and case note review of photographs of the hands revealed a range of severity of the hand syndactyly in those with unoperated hands, similar to previous reports (Hoover *et al.,* 1970, Upton 1991). However, the deformities were asymmetric in six cases (5, 22, 26, 30, 40 and 41). Three of these were particularly interesting as they demonstrated unilateral polydactyly of the little finger which required additional surgical intervention (cases 5, 22 and 40). An example is shown in Figure 4.2.

A feature which has not been previously reported was the frequent occurrence of anomalous epiphyses (or possibly pseudoepiphyses) at the distal aspect of the proximal phalanges of the index, middle, ring and little fingers in younger children. The serial studies suggest that they appear to preceed the development of longitudinal fusions between adjacent phalanges (symphalangism).

FIGURE 4.2 PHOTOGRAPHS OF THE HANDS OF CASE 40 AGE FIVE YEARS



Duplication of the little finger of the Left hand (arrowed), the right hand has no duplication.

THE FEET

Anomalies of the feet were present in all cases. Clinical examination revealed syndactyly with broad feet. The soft tissue anomalies included callosities on the sole of the foot, particularly at the site of the head of the second metatarsal. These were universally present in all cases who were walking, and were particularly notable in two cases (no's. 27 and 35). Clinical examination of the big toe revealed that it often had a varus deformity and was proximally positioned, the position being more abnormal in the older cases. An example is shown in Figure 4.3. The feet anomalies were clinically asymmetric in two cases (case no's 23 and 42), an example is shown in Figure 4.5.

Sixty three radiographs were reviewed from thirty eight cases, seventeen cases undergoing serial studies. No film was thought to be normal. Serial studies had two films in ten cases (no's 5,6,11,14,16,24,31,34,39 and 40), three films in six cases (no's 8,9,13,15, 27 and 35) and four films for case 28.

The radiographs revealed anomalies of the skin and a wide range of anomalies of the skeleton, including fusions of the tarsals, metatarsals, and phalanges, and these are shown in Table 4.2.

The congenital anomalies included syndactyly and incomplete duplication of the 1st metatarsal. In one case complete duplication of the 1st metatarsal occurred, and is shown in Figure 4.4. The syndactyly which was present in every case usually involved the skin only. However, six older cases had developed transverse fusions of the phalanges (cases 4, 9, 14, 20, 27 and 28), producing compound syndactylies. Three of these cases (9,27 and 28) had earlier radiographs without these fusions, so demonstrating progressive fusion. The middle

phalanges were congenitally missing in all but two cases (no's 21 and 35), an example of which is shown in Figure 4.6.

Fusions were present on all radiographs, after the age of two years, with two exceptions. Fusions occurred at all sites apart from the talo-navicular joint which was spared even in the severest cases. In addition to the talo-navicular joint there was also sparing of the 5th metatarsal-cuboid joint in five of the cases with severe tarsal fusions.

There was radiographic evidence that the fusions were progressive in 15/17 of those cases with serial studies. The fusions affecting the tarsal bones started with fusion of the calcaneus and cuboid. The following fusions could not confidently be placed in a particular order as the time interval between each radiograph was too great. However, the following occurred after calcaneo-cuboid fusion: the base of the third metatarsal fused with the lateral cuneform, fusion of the navicular with the medial cuneform. The films of the older cases were so affected by fusions that it was not possible to distinguish the individual sites of fusion within the tarsus.

The phalangeal and metatarsal fusions often commenced at the same time as the tarsal fusions. The phalanges demonstrated symphalangism, but prior to this, anomalous epiphyses (or pseudoepiphyses) were seen at the distal end of an affected proximal phalanx, see Figure 4.6. The progessive fusions affecting case 35 are shown in Figures 4.7. and 4.8. A small area of calcification close to the base of the second proximal phalanx was commonly observed. In cases where there was only a single phalanx of the hallux, it was difficult from its size and position to be sure what this represented. It was thought most likely to be a

laterally positioned anomalous proximal phalanx, but it could represent duplication of the 2nd proximal phalanx, or ectopic calcification.

The clinical significance of the anomalies of the feet were apparent in early childhood, with walking in most children commencing later than the usual range of eleven to fourteen months (Hull and Johnston, 1987). This is shown in Table 4.3. In addition to the cases shown in Table 4.3, eight cases were reported by their parents as never crawling but "bottom shuffling".

The clinical management of the feet in most cases was undertaken by Orthopaedic Departments close to the home of each affected individual. This resulted in a wide range of management, with the aim of improving mobility and ensuring that footwear could be used. Treatments included the provision of physiotherapy, orthopaedic footwear and surgery. The orthopaedic footwear consisted of "Piedro" boots (registered trademark), and these were worn sucessfully in all fourteen cases that they were used, see Table 4.3. However, ten further cases reported that only training shoes were worn as these were the only shoes which were sufficiently wide.

Surgery had been undertaken in eleven cases with the aim of improving function, and the ability to wear normal footwear. A range of operations had been undertaken to both the skeleton and to the nails, and these are detailed in Table 4.4.

TABLE 4.2 ANOMALIES OF THE FEET IN APERT SYNDROME
38 cases, None normal.

Anomaly	No. of cases
HALLUX	
Distal phalanx broad	20
Distal phalanx extra epiphysis	1
Distal phalanx laterally positioned	1
Proximal phalanx laterally positioned	16
Proximal phalanx hypoplastic	14
Proximal phalanx duplicated	4
Proximal phalanx bracket epiphysis	1
Proximal phalanx absent	1
Phalangeal fusion	11
TOES 2-5	
2nd Distal Phalanx attempted duplication	1
Distal phalanx hypoplastic	12
Distal phalanx triangular	6
Middle phalanges absent	36
Proximal phalanx pseudoepiphysis	15
4th Proximal phalanx hypoplastic	2
5th Proximal phalanx "angelwing epiphysis"	1
Phalangeal fusions (symphalangism)	26
Phalangeal fusions (transverse)	6

continued overleaf

TABLE 4.2 ANOMALIES OF THE FEET IN APERT SYNDROME
(continued)

Anomaly	No. of cases
METATARSAL	
1st Metatarsal proximal duplication	15
1st Metatarsal hypoplastic	3
1st Metatarsal distal epiphysis	6
2nd Metatarsal hypoplastic	1
2nd Metatarsal enlarged	2
3rd Metatarsal hypoplastic	3
3rd Metatarsal additional epiphysis	3
4th Metatarsal hypoplastic	1
4th Metatarsal long	1
5th Metatarsal hypoplastic	5
5th Metatarsal proximally positioned	3
Midshaft transverse fusions	2
Proximal transverse fusions	31
Longitudinal fusions (to Tarsals)	26
TARSALS	
Multiple fusions	30
OTHERS	
Os Peroneum	4

TABLE 4.3 CLINICAL SIGNIFICANCE OF FOOT ANOMALIES IN APERT SYNDROME.

Case No.	Age when walking (Months)	Orthopaedic footwear	Surgery
1.	19	Y	N
2.	16	Y	N
3.	18	Y	N
4.	17	Y	N
5.	BOTTOM SHUFFLING	N	N
6.	23	Y	N
7.	17	N	N
8.	18	N	N
9.	19	Y	Y
10.	21	N	N
11.	18	N	N
12.	16	Y	Y
13.	19	N	N
14.	22	N	N
15.	23	N	N
16.	18	N	N
17.	20	N	N
18.	17	N	N
19.	31	N	N
20.	15	Y	Y
21.	22	N	N
22.	34	N	Y
23.	CRAWLING	N	N
24.	17	N	N
25.	18	Y	Y
26.	32	Y	Y
27.	19	N	Y
28.	16	N	N
29.	25	N	Y
30.	CRAWLING	N	N

continued overleaf

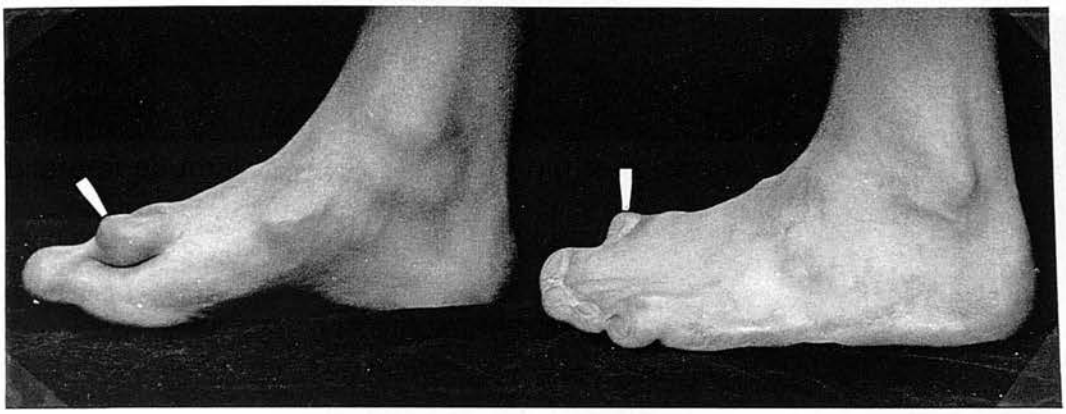
TABLE 4.3 CLINICAL SIGNIFICANCE OF FOOT ANOMALIES IN APERT SYNDROME.
(continued)

Case No.	Age when walking (Months)	Orthopaedic footwear	Surgery
31.	17	Y	Y
32.	19	N	N
33.	17	N	N
34.	24	Y	Y
35.	17	N	N
36.	10	Y	N
37.	13	N	N
38.	18	N	N
39.	20	N	N
40.	19	N	N
41.	NOT YET CRAWLING	N	N
42	NOT YET CRAWLING	N	N
43.	16	Y	Y
Total		14	11

TABLE 4.4 SURGICAL PROCEDURES ON THE FEET IN APERT SYNDROME.

Case No.	Procedure	Age at onset of surgery (years)
9.	Bilateral amputation of distal 2nd Metatarsals	4
9.	Bilateral amputation of little toes	9
12.	Release syndactyly 3rd web	3
12.	Trimming of osteophyte Right Talus	13
20.	Amputation right little toe	7
22.	Right ingrowing toe-nail phenolisation	2
25.	Left 1st metatarsal osteotomy	6
26.	Bilateral syndactyly release of 1st web space	2
27.	Amputation of right hallux	9
29.	Trimming of osteophyte right 2nd metatarsal	8
31.	Bilateral ingrowing toe-nail phenolisation	5
34.	Bilateral amputation of little toes	11
43.	Bilateral amputation of big toes	8

FIGURE 4.3 PHOTOGRAPH OF THE FEET OF CASE 43 AGE TEN YEARS

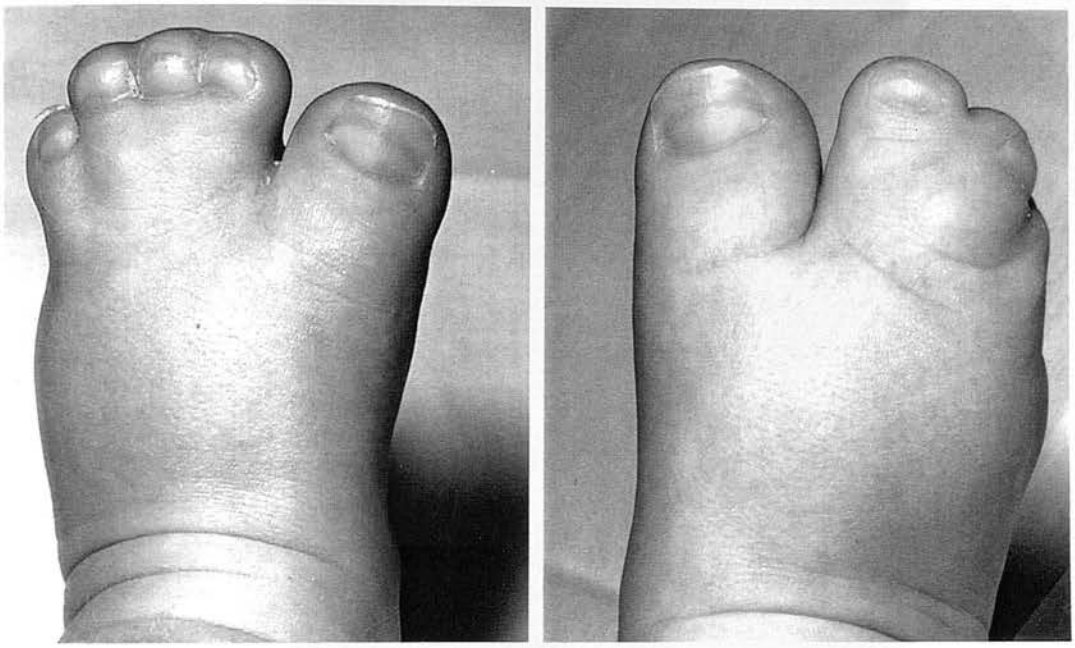


Bilateral anomalous position of the big toes (arrowed)

FIGURE 4.4 RADIOGRAPH OF THE LEFT FOOT OF CASE 42 AGE SIX MONTHS

Complete duplication of the first metatarsals (arrowed)

FIGURE 4.5 PHOTOGRAPH OF THE FEET OF CASE 23 AGE SIX MONTHS



Asymmetric anomalies

FIGURE 4.6 RADIOGRAPHS OF THE FEET OF CASE 21 AGE FOUR YEARS

Middle phalanx left third digit (heavy arrow)
Anomalous epiphyses on the distal aspect of the proximal phalanx (fine arrows)

FIGURE 4.7 SERIAL RADIOGRAPHS OF CASE 35

a.Three months

b. Nine years

Progressive fusion of the tarsals and phalanges.

FIGURE 4.8 RADIOGRAPH OF THE RIGHT FOOT OF CASE 35 AGE TWELVE YEARS

Further progressive fusion of the metatarsals
Note presence of Os peroneum (arrowed)

THE ELBOWS

Clinical examination of the elbows was performed in forty three cases and revealed a reduced range of movement in twenty six cases. The loss of movement universally affected extension/flexion, but pronation/suppination was also reduced in 14/26 cases. Fixed flexion deformity greater than ten degrees was observed in twelve cases, an example of which is shown in Figure 4.10. Five cases were noted to have marked dimples over the elbow (cases 1, 5, 23, 41 and 42). All of these cases were less than three years old and an example is shown in Figure 4.9.

The results of the radiographic examination of the elbows were studied in thirty nine cases. Three radiographs were discarded, leaving a total of thirty six cases. Serial studies were available for two cases (no's 22 and 28). Eleven cases were judged to be normal. Two cases were noted to have asymmetrical anomalies. A total of thirty seven anomalies were seen in twenty five cases, demonstrating a wide range of radiographic abnormalities. The types of anomalies and their incidence are shown in Table 4.5. The age range at the time of the first examination ranged from three months to twenty years, the median age being seven years.

Radial head dislocation or subluxation, and epiphyseal delay were the most common anomalies, an example of which is shown in Figure 4.11. Synostosis was seen in four cases and affected the humero-ulnar joint in four cases (no's 29,31,35 and 37), with the radio-humeral joint also affected in one case (no. 35). There was no evidence of progressive fusions in either of the serial studies.

TABLE 4.5 ANOMALIES OF THE ELBOWS

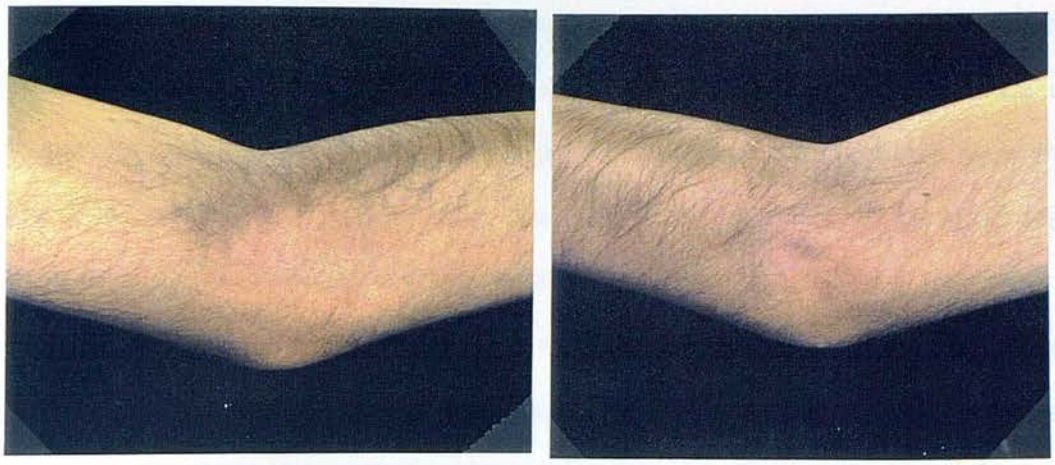
36 cases, 11 normal, 2 cases were asymmetrical.

Anomalies	No. of cases
Epiphyseal delay	11
Radial head subluxation	10
Radial head dislocation	6
Humeral head subluxation	1
Humero-ulnar synostosis	4
Humero-radial synostosis	1
Radial head "mushrooming"	2
Ulna shaft "square"	1
Absent medial humeral epicondyle	1

FIGURE 4.9 PHOTOGRAPH OF CASE 1 AGE FOURTEEN MONTHS

Dimples over the elbows and the shoulders (arrowed)

FIGURE 4.10 PHOTOGRAPH OF THE ELBOWS OF CASE 37 AGE ELEVEN YEARS



Bilateral fixed flexion deformity

FIGURE 4.11RADIOGRAPH OF THE ELBOW OF CASE 31 AT TEN YEARS

Radial head subluxation
Reduced joint space humero-ulnar joint

THE SHOULDERS

Clinical examination of the shoulders was performed in forty three cases. The most striking feature was the "squared off" appearance of the shoulders and an example is shown in Figure 4.12. Dimples over the shoulder joint were seen in two cases (no's 1 and 42), both aged less than two years, and an example is shown in Figure 4.9.

There was a reduced range of movement in thirty six cases, those which were normal were all aged less than four years. Abduction was reduced by more than ten degrees, the most severely affected case (no. 29) could only abduct to sixty degrees. Six cases (no's 10,11,14,25,29 and 34) had reduction of flexion/extension of greater than twenty degrees. All cases were symmetrical. The functional significance of the anomalies was not readily apparent. Difficulty combing their own hair was occasionally reported, but patients did not report any other limitations.

The results of the radiological examinations were available for both shoulders in thirty two cases. In two cases the radiographs were too poor for assessment and so were discarded leaving thirty cases. The age at the time of the first radiograph ranged from three months to nineteen years, with a median of seven years. Serial studies were available for two cases (no's 7 and 28). Four cases were radiographically normal (cases 2,7,19 and 41), the remainder demonstrated a range of anomalies which are summarised in Table 4.6.

Enlargement of the acromial head, hypoplastic glenoid and anomalies of the epiphysis of the humeral head were the most common shoulder anomalies. Examples of these are shown in Figures 4.12 and 4.13. No fusions were seen in any radiograph. A review of the findings of the

serial studies was interesting in that case 7 had radiographs at fourteen months which were normal, and later views at age nine years demonstated the development of a hypoplastic glenoid and epiphyseal delay. Case 28 had radiographs at three months which demonstrated a wide humeral head, but further radiographs at age 10 years demonstrated the additional development of varus deformity of the humeral head. These cases demonstrated increasing severity of the anomalies with increasing age, and this occurred in the absence of fusions.

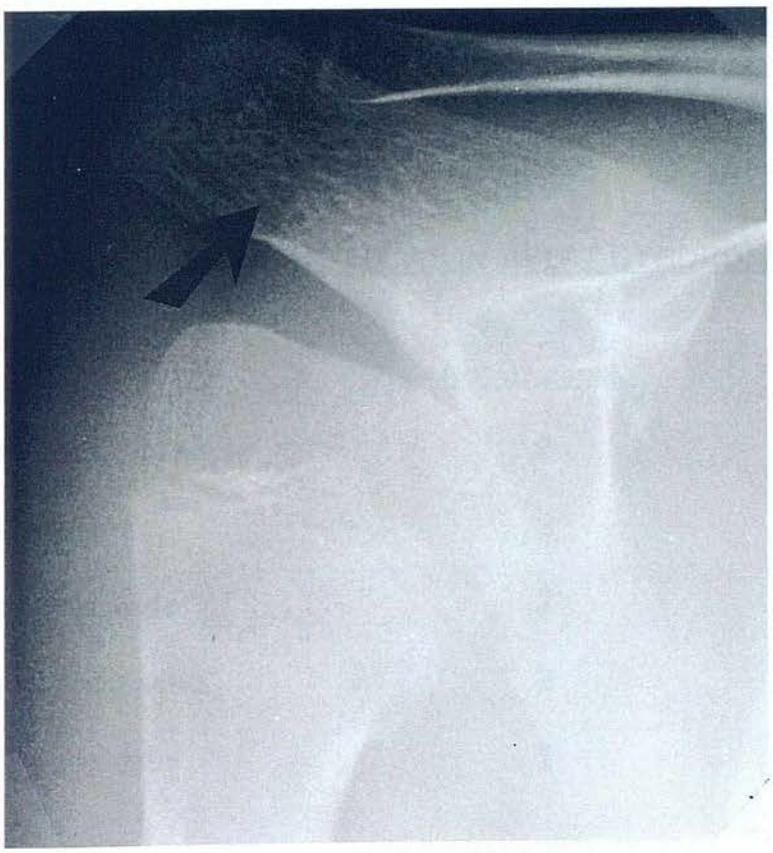
TABLE 4.6 ANOMALIES OF THE SHOULDERS
30 cases, 1 asymmetrical, 4 cases normal.

Anomalies	No. of cases
Varus deformity of the humeral head	11
Flattening of the humeral head	8
Subluxation of Humeral head	3
Enlarged acromium	16
Hypoplastic glenoid	12
Epiphyseal delay	8
Abnormal acromio-clavicular joint	1

FIGURE 4.12 PHOTOGRAPH OF CASE 37 AGE ELEVEN YEARS

Squared off appearance of the shoulders

FIGURE 4.13 RADIOGRAPH OF THE LEFT SHOULDER OF CASE 31 AGE 10 YEARS



Flat humeral head
Enlarged acromium (arrowed)

THE KNEES

Clinical examination of the knees was unremarkable with no clinically obvious examples of valgus or varus deformities.

Radiological examination was available in four cases (no's 15, 25, 31 and 41) and was normal in all four.

THE PELVIS

Clinical examination of the hips was unremarkable.

Radiographs of the pelvis were available for six cases (no's 15, 28, 29, 31, 39 and 41). Four cases were female and two male. The age range was from three months to seventeen years.

All six of these cases demonstrated at least one anomaly affecting either the upper femur or the pelvis, an example is shown in Figure 4.14. The full range of anomalies are shown in Table 4.7.

TABLE 4.7 ANOMALIES OF THE PELVIS IN APERT SYNDROME
6 cases. None normal.

Anomaly	No. of cases
Greater trochanter enlarged	3
Femoral neck short	3
Symphysis pubis wide	2
Acetabulum hypoplastic	2
Pubic rami hypoplastic	1

FIGURE 4.14 RADIOGRAPH OF THE PELVIS OF CASE 31 AGE 10 YEARS

Short femoral neck
Enlarged greater trochanters (arrowed)
Bilateral acetabular dysplasia

OTHER RADIOGRAPHS

Chest radiographs were available for almost all the cases, but many films were of poor quality and so were discarded. However, examination was possible in twelve cases (case no's 4,6,7,13,15,17,18,21,25,27,28 and 36). No anomalies were seen on these twelve radiographs.

Radiographs of the ankle were available for two cases (no's 27 and 29). Both revealed anomalies with flattened malleoli case 27, and multiple fusions in case 29.

Radiographs of the humerus were obtained in two cases (no's 15 and 24). Case 15 had a double upper femoral epiphysis, unilaterally, while case 24 was normal.

GENETICS

The mutations have been identified in fourteen cases. Examples of both the C934G and the C937G genotypes have been identified and are shown below in Table 4.8.

TABLE 4.8 THE MUTATIONS OF CASES OF APERT SYNDROME.

Mutation	Amino Acid Change
C934G	Ser252Trp
C937G	Pro253Arg

C934G

Case No.	Sex	Age (Years)
3.	F	4
4.	M	13
14.	F	17
16.	F	3
21.	F	4
22.	F	5
24.	M	2
31.	F	10
43.	M	20

C937G

Case No.	Sex	Age (Years)
15.	F	2
17.	M	2
28.	M	10
33.	M	2
36.	M	5

DISCUSSION

CLINICAL EXAMINATION

The finding of shortness of stature in the four girls who were skeletally mature is similar to the results of a previous larger study (Cohen and Kreiborg, 1993b). Conversely, the finding of no obvious change in percentiles for height of boys and skeletally immature girls is different to this earlier study, in which a biphasic decelaration of linear growth was described for both sexes (Cohen and Kreiborg, 1993b). However, there were differences in final heights between the sexes with males above twenty-fifth centile, but females only above the tenth centile, which is a similar pattern to the results of this study. The reduced final height has been proposed to be the result of femoral shortening, which is thought to occur as a result of the same process which produces rhizomelic shortening of the humerus (Cohen and Kreiborg, 1993c).

The difference between the males and skeletally immature females obtained in this study, and those of Cohen and Kreiborg (1993b), could be the result of individual variation, or reflect the small sample numbers in this study. Also, the study of Cohen and Kreiborg (1993b), used mixed American and Danish populations, but applied American normal standards (Hamill *et al.*, 1979) to all cases, so this too could be a factor. Although both studies used cross-sectional height measurements, studies with longitudinal height measurements would clarify the growth pattern in both sexes. To enable this to be undertaken, height and weight measurements should be recorded at all hospital visits.

The total body weight centiles were unremarkable, and no previous study of this could be found, except for one previous study which focussed on post-mortem brain weight rather than total body weight measurements (Cohen and Kreiborg, 1993b).

The few visceral anomalies in this population is surprising given that there have been many previous reports of a wide range of anomalies, particularly affecting the cardiovascular and genito-urinary systems, in Apert syndrome (Cohen and Kreiborg, 1993a). The incidence of both cardiovascular and genito-urinary anomalies has been reported to be 10%, while respiratory and gastrointestinal anomalies have a reported incidence of 1.5% (Cohen and Kreiborg, 1993a). Extensive review of these anomalies has shown many to be isolated cases (Cohen and Kreiborg, 1993a). A commonly reported anomaly, shown from autopsy studies, and not identified in this population, is a completely cartilagenous trachea, which has been reported on eight occasions (Cohen and Kreiborg, 1992). It is noteworthy that in all of those reported eight cases the anomaly was unsuspected clinically.

The anomalies of pyloric stenosis and ventricular septal defect identified in this series have both been previously reported in association with Apert syndrome (Blank, 1960; Cohen, 1972). However, gut malrotation and talipes equinovarus appear to be new findings.

Other anomalies include acneform eruption which is a well recognized feature of Apert syndrome. This resembles acne vulgaris clinically, but differs in that the distribution is more extensive, often affecting the limbs (Krafchik, 1991). The presence of this in all teenagers here is therefore expected, but why only one case (case no. 25) had forearm involvement is unclear.

The findings by Thompson *et al.* 1996, were similar to earlier reports both in respect of the incidence of fusions in this condition, and the levels affected (Hemmer *et al.,* 1987; Kreiborg *et al.,* 1992). The finding of fusions predominantly at the C5/C6 level and the incidence of 63% is in marked contrast to the findings in the normal population where the level affected is most commonly C2/C3 (Brown *et al.,* 1964) and the incidence has been reported to be 0.5% to 3% (Shands and Bundens, 1956; Gray *et al.,* 1964).

These findings also differ from the other complex craniosynostosis syndromes of Pfeiffer and Saethre-Chotzen syndrome where C2/C3 is the commonest level for fusions (Chapters 3 and 5).

There is evidence from serial studies in 10/18 cases that the fusions are progressive in this condition, which is in keeping with fusions at other sites of the extracranial skeleton (Schauerte and St-Aubin, 1966; Beligere *et al.,* 1981), and with the findings in the complex craniosynostosis syndromes (Chapters Two, Three and Five).

The pattern of fusion was interesting in that in all twenty cases where the posterior elements were fused, the vertebral bodies had already undergone fusion. There were however eighteen cases where vertebral body fusion had occurred but the posterior elements were normal. This pattern was similar to the fusions at C5/C6 level in Crouzon syndrome, but was the reverse of the pattern of fusion at the C2/C3 level in Crouzon syndrome (Chapter Two).

The incidence of fusions at 37/59 cases is higher than the 10/50 cases with fusions in Crouzon syndrome, but similar to the 18/25 cases

of Pfeiffer syndrome with fusions. This is curious as all these syndromes can result from mutations of the FGFR 2 gene (Reardon *et al.,* 1994; Wilkie *et al.*, 1995b; Rutland *et al.,* 1995). Different levels of fusion also exist in these three syndromes. Why these differences exist is currently unclear.

THE HANDS

The anatomy of the hands in Apert syndrome is grossly abnormal with anomalies not only of the bones but also the tendons, nerves and vasculature (Green, 1982). The normal anatomy of the hands is much more disturbed than in Pfeiffer or Crouzon syndrome. The degree of syndactyly present in each hand, as it affects the 1st and 4th web spaces is used to classify the severity of the hand deformity (Upton, 1991).

The severity of the hand anomalies was unrelated to the craniofacial manifestations. The finding of asymmetry of the hands is significant because it disproves previous reports which state that the syndactyly is always symmetrical (Park and Powers, 1920; Upton,1991). The finding of unilateral ulnar polydactyly in three cases emphasises this point. It is noteable that there is no association between the development of polydactyly and the degree of syndactyly, so clinical examination of an infant cannot be used as a guide for the presence of this anomaly. The most common digit to display this polydactyly is the little finger. This anomaly, has been reported in association with over forty abnormalities (Wood, 1988), but has only recently become recognised in association with Apert syndrome (Cohen and Kreiborg, 1995).

The fusions, like those in the hands of cases of Pfeiffer syndrome, were progressive and affected the carpals, metacarpals, and the phalanges longitudinally. If digits remained undivided then progressive fusion occurred transversely. The radiographic evidence implies that surgical intervention to correct the syndactyly should be performed early in life, not only to promote the development of finger function (Barot and Caplan, 1986), but also to prevent the formation of transverse fusions between adjacent phalanges.

THE FEET

A wide range of anomalies have been demonstrated in the feet, and this study extends the current knowledge of these. All cases had anomalies of the feet which were evident at birth. These were usually symmetrical but two obvious exceptions were seen. This is in contrast to the previous reports which emphasised symmetry of the feet (Park and Powers, 1920; Blank, 1960; Feinstein and Rubin, 1978; Mason *et al.,* 1990). The anomalous positions of the big toes was associated with the development of the callosities on the soles of the feet in unusual positions in all those cases who were walking. These have been described previously (Mah *et al.,* 1991; Upton, 1991). It was notable that in the two cases with large callosities, the 2nd metatarsals and phalanges had undergone enlargement in response to the weight bearing stresses placed upon those parts of skeleton in response to walking (cases 27 and 35). This result does not appear to have been previously described. The presence of callosities contributed to the difficulties of obtaining footwear.

The radiographic findings of progressive fusions confirm earlier reports (Schauerte and St-Aubin, 1966; Mah *et al.,* 1991). The sites, with calcaneo-cuboid coalition starting first, were the same as previous reports (Schauerte and St-Aubin, 1966), but an order for the remaining tarsal fusions could not be confidently established from the serial radiographs available in this study.

The finding of absence of three phalanges in each of toes 2-5 in Apert syndrome is well recognised (Schauerte and St-Aubin, 1966; Mah *et al.,* 1991; Taybi and Lachman, 1996). However, it has previously been reported that it is the distal phalanges that were missing (Mah *et al.,* 1991), rather than the middle phalanges, as in these cases. The presence of three phalanges in two of these cases, appear to be morphologically middle phalanges (see Figure 4.6), which suggests that it is these rather than distal phalanges which are missing in all the other cases.

The presence of the anomalous epiphyses at the distal end of the proximal phalanges, is similar to the findings in the hands. These have been observed prior to the onset of symphalangism (see Figure 4.6), and while their significance is unclear it is speculative that they may have some role in the subsequent development of symphalangism.

The identification of calcification close to the base of the second metatarsal, and difficulties ascertaining its origin has not been previously reported, although it has been established that the proximal phalanx of the hallux can be laterally positioned. The phalangeal fusions were similar to previous descriptions (Schauerte and St-Aubin, 1966), but the presence of epiphyses at the distal aspect of the proximal phalanges, prior to the onset of symphalangism has not been reported.

The pattern of proximal duplication of the first metatarsal seen in this series has been well recognised previously (Schauerte and St-Aubin, 1966). However, the incidence of metatarsal fusions with 31/38 cases affected is different to a previous report where fusions were not commonly observed at this site (Mah *et al.,* 1991)

The presence of Os peroneum, an accessory bone located in the peroneus longus tendon, has been previously reported (Schauerte and St-Aubin, 1966). This has been estimated to occur in 7% of the normal population (Shands, 1931), however it was observed in 4/11 cases in this population who were aged at least ten years and who underwent radiological examination of the feet. An example is shown in Figure 4.8.

Clinically, anomalies of the feet have been shown to affect almost all of those with this condition. Walking, and difficulties in obtaining footwear were observed. The time of walking for a large group with Apert syndrome has not been previously recorded. Despite variation in the normal population, which can range from eleven to fourteen months (Hull and Johnston, 1987), it appears that in most of these cases walking is commonly delayed beyond the normal range (see Table 4.3). The delay was occasionally severe, and was delayed until two years of age in 5/43 cases, and walking occurred as late as thirty four months.

The need for 14/43 cases to have orthopaedic footwear highlights that obtaining suitable footwear is difficult. However, because this aspect of clinical management is often performed in many local district hospitals rather than in a single centre, the significance is not readily apparent.

The eleven cases who underwent surgery is larger than any previously recorded series; four cases (Mah *et al.,* 1991), two cases (Dell and Shephard, 1981), and a single case (Pflanzer, 1978; Krauspe, 1996).

The range of surgical procedures undertaken was wide with seven cases undergoing surgery to the feet at local hospitals. The most common reason for surgery was to amputate toes or osteophytes which were interfering with footwear. However, no cases of surgery to the callosities were recorded, despite the fact that it has been suggested that this be undertaken (Mah *et al.,* 1991).

In summary, the clinical significance of the anomalies of the feet in Apert syndrome is greater for most cases than the current medical literature suggested. This is due to the focus on the management of the craniofacial and hand anomalies. The clinical significance of anomalies of the feet in this condition have been recognised (Mah *et al.,* 1991; Krauspe, 1996), with the recommendation that regular Orthopaedic review at a specialist centre be undertaken.

THE ELBOWS

Anomalies of the skeletal morphology and fusions have been shown to occur commonly at the elbow in Apert syndrome (Cohen and Kreiborg, 1993b; Wood *et al.,* 1995).

The five cases with skin dimples over their elbows were all aged less than three years. This is in keeping with a previous study (Cohen and Kreiborg, 1993b), and they have been reported to disappear with increasing age during childhood. The significance of these dimples is not known. Of the five cases two had undergone radiographic examination of the elbows. These radiographs were inconsistent with case 1 demonstrating delayed epiphysis formation but case 42 was normal.

Long term follow up of these cases will help establish if there is any subsequent development of a pattern of anomalies seen.

The incidence of clinically detectable loss of movement in 26/43 cases compares with previous reports which found movement reduced in 26/28 cases (Cohen and Kreiborg, 1993b), 14/19 cases (Kasser and Upton, 1991), 7/10 cases (Beligere *et al.,* 1981) and 6/9 (Wood *et al.,* 1995). The difference between the incidence of limitation of movement of the elbow in this study, (as well as those of Beligere *et al.* 1981; Kasser and Upton, 1991; Wood *et al.,* 1995), and the almost universal finding of limited movement by Cohen and Kreiborg, (1993c) is probably due to the ages of the populations studied. In this study, only children were examined, but Cohen and Kreiborg's study involved mostly adults. These results taken together provide evidence that at the elbows, limitation of movement develops during childhood, almost universally, in this syndrome.

The finding of normal radiographs in 11/36 cases is similar to the incidence of radiographic anomalies in a previous report (Upton, 1991). The anomalies in this present series are particularly interesting. Synostosis was observed in 4/33 cases, always affecting the humero-ulnar joint and also the humero-radial joint in one case. Previous reports of synostosis in Apert syndrome have nearly always affected the humero-radial joint (Cohen and Kreiborg, 1993b). Radio-ulnar synostosis has also been reported (Berlotti and Boidi Trotti, 1915). Humero-ulnar synostosis has been described but the number of cases is unclear (Upton, 1991). The reason for this cluster of cases with synosotosis primarily affecting what would appear to be a rare site, is unclear.

The ages of those cases affected by synostosis ranged from eleven years to seventeen years, although only one is skeletally mature. The previously reported youngest age in which synostosis was observed was at eight years (Cohen and Kreiborg, 1993b). The timing of the development of synostosis is currently unclear, but these results confirm that synososis of the elbow in Apert syndrome can occur in the skeletally immature.

Finally, the anomalies of the elbow have been classified into two groups on the basis of their appearance of the radial head and the angulation of the radial neck (Upton, 1991). The cases in the present study did not comply with the proposed classification, suggesting there is no basis for its continued use.

THE SHOULDERS

The results of this study show that anomalies of the shoulders are very common, and that there are clinical consequences which follow as a result of these. The two cases with dimples over the shoulder were both aged less than two years. These have been reported in children as old as twelve years, but disappear during childhood (Cohen and Kreiborg, 1993c). Their significance is not known, but it is interesting that these cases both demonstrated additional anomalies. One case had hypoplasia of the glenoid and epiphyseal delay of the humerus, while the other had an abnormally broad upper humerus.

Reduction in movement was found 36/43 cases, and occurred in all cases aged four years or more. This compares to a report which demonstrated reduction in movement at the shoulder in 36/38 cases of

a mixed adult and child population (Cohen and Kreiborg, 1993c). The results of their study in children is similar to an earlier study of children which reported radiographic anomalies in 6/9 cases (Wood *et al.,* 1995). However, this present study contrasts with the earlier study in that no cases demonstrated a reduced range of motion during the clinical examination in children with normal radiographs (Wood *et al.,* 1995).

The radiographic anomalies were detected in 26/30 cases, with the four normal cases all under three years of age at the time of the radiograph. This confirms an earlier report which found that the shoulders were radiographically normal at birth but that anomalies developed with growth (Upton, 1991). This concept is supported by the findings in cases 7 and 28 which demonstrated radiographic anomalies which could not have been predicted from the previous radiographs. An earlier study of the shoulders of children with Apert syndrome found radiographic anomalies in 6/9 cases (Wood *et al.,* 1995), but did not give the ages of the children with normal radiographs. The conclusion from the results of this study, along with the findings of earlier studies on children and adults, is that the shoulders can be normal at birth but that anomalies leading to reduced movement develop during childhood.

The common anomalies were enlarged acromium, hypoplasia of the glenoid, and humeral epiphyseal delay. These have been previously reported (Upton, 1991; Cohen and Kreiborg, 1993b; Wood *et al.,* 1995), although glenoid dysplasia has been stated to be the most common anomaly (Upton, 1991; Kasser and Upton, 1991). The acromium has been reported to be normal, with prominence relative to anomalies of other components of the shoulder (Upton, 1991). The

observations in this study disagree with this as it appeared to be truly enlarged from normal in some cases (see Figure 4.13), which confirms a previous report (Kasser and Upton, 1991).

It was notable that there was no cases of fusion in this series. This has been previously reported as occurring at the gleno-humeral joint in a single case (Yohenobu *et al.,* 1982). The conclusion must be that fusion at the shoulder is very rare.

On the basis of the high frequency of anomalies producing loss of function, during childhood, it is interesting to speculate whether orthopaedic replacement of the shoulder might be beneficial to some of these cases once they have developed skeletal maturity.

THE KNEES

There is very little published regarding the knees in Apert syndrome. They are not mentioned in some series (Blank, 1960) or not investigated as there was no functional loss (Upton, 1991). This absence of reported anomalies and the absence of clinical findings in this present series is in marked contrast to the report of valgus deformity in 16/38 cases, and one case with joint ankylosis (Cohen and Kreiborg, 1993c).

The four cases in this series who had normal radiological examinations, tentatively suggests that the unremarkable clinical examination of the knee does not conceal any commonly occurring radiological anomaly. No previous study of the radiological examination of the knees could be found, and this includes the series with cases demonstrating clinical anomalies (Cohen and Kreiborg, 1993c).

In summary it would appear that the knee is rarely affected in Apert syndrome. The reason for the rarity of anomalies is surprising both when compared to the frequency of anomalies of other joints in Apert syndrome, and to the findings of anomalies at this site in other syndromes. However, this study and all previous studies are limited in the investigation of this site, and so further cases are needed to confirm these findings.

THE PELVIS

The normal clinical examination of the hips in these cases is similar to the findings of a previous study (Upton, 1991). These findings are different to a report which found altered gait in a patient with unilateral hip dislocation who was also unable to walk (Cohen and Kreiborg, 1993c). This difference may be due to different ages of the populations studied since three of the cases in this study were aged under three years at the time of the radiograph, and the case of Cohen and Kreiborg (1993c), was an adult.

The radiographic anomalies seen in this study confirm the previous report of anomalies of the acetabulum, and femoral head and neck (Cohen and Kreiborg, 1993c). Pelvic radiographs demonstrating anomalies have also been reported but the incidence and the types of anomalies seen has not been stated (Blank, 1960).

The pelvis and upper femur have demonstrated radiographic anomalies in all cases, although there were no clinical findings to suggest these. Radiographic anomalies at this site may therefore be more common than

is currently appreciated, but further studies are required to determine whether this is so.

OTHER VIEWS

Twelve chest radiographs were reviewed but no anomalies were seen. No previous reports of rib anomalies were found, although fusions and hemivertebrae of the thoracic and lumbar spine have been reported (Cohen and Kreiborg, 1993c).

Radiographs of the ankle were available for two cases (no's 27 and 29). Both revealed anomalies with flat malleoli in case 27, and multiple fusions in case 29. No previous reports were found of anomalies at this site, this may be due the joint being obscurred during radiological investigation of the feet. These cases suggest that anomalies can occur at this site, but their incidence remains unknown.

The radiographs of the humerus revealed a unilateral double epiphysis in one case but no other anomaly. This compares with previous reports which have shown shortening of the humerus to be a common feature (Blank, 1960; Cohen and Kreiborg, 1993c). This difference could be explained by the fact that these two cases were aged less than two years at the time of their radiographic examinations.

GENETICS

Apert syndrome phenotypes usually result from one of only three mutations (Wilkie *et al.,* 1995b; Oldridge *et al.,* 1997), with the two most common of these resulting from specific missense substitutions

involving adjacent amino acids (Ser252Trp or Pro253Arg) in the linker region between the second and third extracellular domains of the FGFR 2 (Wilkie *et al.,* 1995b). This makes investigation of phenotypic differences using the two genotypes to which most cases of Apert syndrome belong, more staightforward than the investigation of phenotypic differences of all the different Crouzon and Pfeiffer syndrome genotypes.

It has been reported that there are significant phenotypic differences in the incidence of cleft palate and the severity of hand syndactyly between the two mutations (Slaney *et al.,* 1996), while another study found no phenotypic differences between the two mutations (Park *et al.*, 1995b). However, neither of these studies included detailed examination of the skeletal morphology.

The two groups have nine cases with the C934G mutation and five cases with the C937G mutation. The groups are not well matched for age and sex, with the C937G group having 4/5 members male, and only a single case older than five years (see Table 4.8). The age difference is important since many anomalies are related to growth and become increasingly severe with time, so caution will be required in interpreting results. Comparison of the elbow and shoulder radiographs could not be undertaken because the age differences in the populations was too great.

The shoulder radiographs of the C937G mutation group were available for four cases, none was normal. Case 36 was the most severely affected with a hypoplastic glenoid and flattening of the humeral heads. Cases 15 and17 only had epiphyseal delay, while case 28 had flattening of the humeral heads. The C934G group had radiographs of the

shoulder in five cases. Case 31 was the most severely affected with subluxation of the humerus, an enlarged acromium and a hypoplastic glenoid. Cases 4 and 14 both had an enlarged acromium and varus deformity of the humerus. Cases 22 and 24 had both epiphyseal delay and hypoplastic glenoids.

The elbow radiographs of the C937G mutation group were available for four cases and were normal in two cases, including a ten year old. The other anomalies consisted of epiphyseal delay in one case and radial head subluxation in the other. This compares to the C934G mutation group, where radiographs were available for five cases, and showed that case 31 had synostosis, cases 4, 21, 22 had dislocated or subluxed radial heads and abnormal epiphyses, while only case 3 (age just 3 years), was normal.

These findings tentatively suggest that there may be phenotypic differences at the elbow, but many more cases are required to establish this, and the samples will need to be better matched for age.

CHAPTER FIVE

CHAPTER FIVE

THE SAETHRE-CHOTZEN SYNDROME

This condition has a particularly variable presentation which can make establishing the diagnosis in an affected individual (which is made on the clinical features) very difficult. As a result although thirty two cases of Saethre-Chotzen syndrome were identified from the database of the Craniofacial Centre, three cases were excluded from the results because of uncertainty regarding the diagnosis.

A total of twenty nine cases had their diagnosis made on the basis of their phenotypic appearance after clinical examination (by the author). The important clinical features were cranial and facial asymmetry with blepharoptosis and low hair line and syndactyly of the fingers and toes. All cases were also examined both by senior surgical staff of the Craniofacial Centre and a Clinical Geneticist who agreed with the diagnosis in all twenty nine cases.

The patients were aged from two months to seventeen years at the time of this review. There were twenty females and nine males, and the cases included two sets of siblings (cases 16 and 26, and cases 24 and 25). A further twenty one patients were known to have an affected parent. This is important since the large number of familial cases in this population is to be expected of the condition because there are few recorded sporadic cases. This provides indirect evidence that this is indeed a Saethre-Chotzen population.

All patients attending Great Ormond Street Hospital during the period March 1995 - April 1996 were interviewed along with their parents to review the medical history and to perform a clinical examination

including height and weight measurements. The height and weight measurements were compared to reported normal values (Tanner *et al.,* 1966) and compared with birth weight and any previously recorded values.

This clinical examination was supplemented by prospective radiological examination, and by review of existing medical and radiological records. The patients were each assigned a number and the results of each clinical and radiological investigation recorded. The radiological examinations are shown in shown in Table 5.1.

RESULTS

CLINICAL EXAMINATION

A clinical examination was performed in all cases. The locomotor examination revealed no loss of movement at any of the joints. There were no obvious deficiencies in height or weight. This was confirmed in eighteen cases where the height and weight records were compared to sex and age standards (Tanner *et al.,* 1966). The boys heights ranged from the twenty-fifth to the ninetieth centile, their weights from the twenty-fifth to the seventy-fifth centile. The girls height ranged from the twenty-fifth to the seventy-fifth centile and their weights were in the same range. There was little difference between the centiles in birth weight and current weight in both boys and girls.

History and case notes revealed a few anomalies, but included hypospadias (case 19), Talipes equinovarus (case 2), Ventricular septal defect (case 8) and congenital inguinal hernia (case 8).

TABLE 5.1 THE CASES AND THEIR RADIOLOGICAL INVESTIGATIONS

Case No.	Sex	Current Age (years)	Cervical Spine	Hands	Feet
1.	F	4	1	-	-
2.	F	6	1	2	-
3.	F	1	1	-	-
4.	F	10	1	2	-
5.	F	4	1	-	-
6.	F	2	2	1	1
7.	M	1	2	1	2
8.	M	5	2	1	1
9.	F	6	2	1	-
10.	F	1	2	1	1
11.	F	4	2	1	1
12.	F	4	3	1	1
13.	M	8	3	1	-
14.	F	17	3	1	-
15.	M	7	2	1	-
16.	M	9	1	1	-
17.	F	4	1	1	-
18.	F	9	1	1	-
19.	M	13	1	1	1
20.	F	11	1	-	1
21.	F	1	1	1	1
22.	F	1	1	1	1
23.	F	1	1	1	1
24.	F	1	1	-	-
25.	M	4	1	-	-
26.	F	9	1	1	-
27.	M	3/12	1	-	-
28.	M	5	1	1	1
29.	F	2	1	1	-
Cases			29	22	12
Films			42	24	13
Serial studies			10	2	1

Cases 2,4,6,11,12,13,16,18,19,21,22 and 28 had radiographic examinations of other sites.
All cases underwent clinical examination.

Clinical examination of twenty nine cases revealed no limitation of movements of the head, and both direct questioning and case note review failed to elicit any symptoms attributable to cervical spine anomalies.

Radiological examination of the cervical spine had been undertaken in all twenty nine cases, in ten of whom sequential studies were available. Forty three sets of radiographs (both lateral and anterior-posterior views) were examined; one set was discarded as the quality was deemed too poor to allow proper assessment. This left forty two radiographs from twenty nine cases. C7 was not visualised in six radiographs studied and C6 not seen clearly in one. The age at the time of the first radiograph ranged from two months to eleven years. The median age for the first radiograph was four years.

Congenital anomalies as well as fusions of both the vertebral bodies and the posterior elements were observed. Anomalies were detected in 14/29 cases. The congenital anomalies consisted of hypoplastic neural arch of C1 which was observed in five cases (no's 8,9,14,15 and 16), and large spinous process of C2 in two cases (no's 7 and 24). Examples of these are shown in Figures 5.1 and 5.2, and Figure 5.3 respectively. No other congenital anomalies, (and in particular no "Butterfly" vertebrae), were seen.

Evidence of fusions was seen in 12/29 cases (41%). The levels of the cervical spine affected by fusions and their relationship to the age of each case is shown in Table 5.2.

The presence of fusions is closely related to the age at the time of the radiograph. Those radiographs obtained before the subject was two

years old had evidence of fusion in only 1/23 cases (case 10). Conversely, after two yeas of age, 14/19 radiographs had evidence of fusion. Only cases 8,13,20,26 and 28 did not show fusion.

The sequential studies performed in ten cases reveal progressive fusion in eight cases (no's 6,9,10,11,12,13,14, and 15). An example of this is shown in Figures 5.1 and 5.2. Four further cases demonstrated the presence of cervical fusions on a single radiograph (no's 16,17,18 and 19). Interestingly, the oldest case in this series (case 14), demonstated evidence of progressive fusion between the ages of ten and thirteen years, however later radiographic examination at age sixteen years revealed no further change.

When considering the level at which fusions were observed, it is clear that C2/C3 is the level most often affected, with fusion in 8/29 cases. Fusion of C4/C5, C5/C6 occurs in two cases, and C1/C2, C3/C4 fusions occur in a single case. There are only two examples of fusions occuring at more than one level in any one case (cases 10 and 14), an example is shown in Figure 5.4.

The pattern of fusion is also notable in that the posterior elements are more frequently fused than the vertebral bodies. It was found that 4/5 cases where there was a hypoplastic neural arch at C1, had associated fusions at C2/3, or subsequently developed fusions at this level. This is shown in Figures 5.1 and 5.2. The case without fusion is presently the youngest and still only four years old.

TABLE 5.2. THE CERVICAL SPINE FUSIONS IN SAETHRE-CHOTZEN SYNDROME.

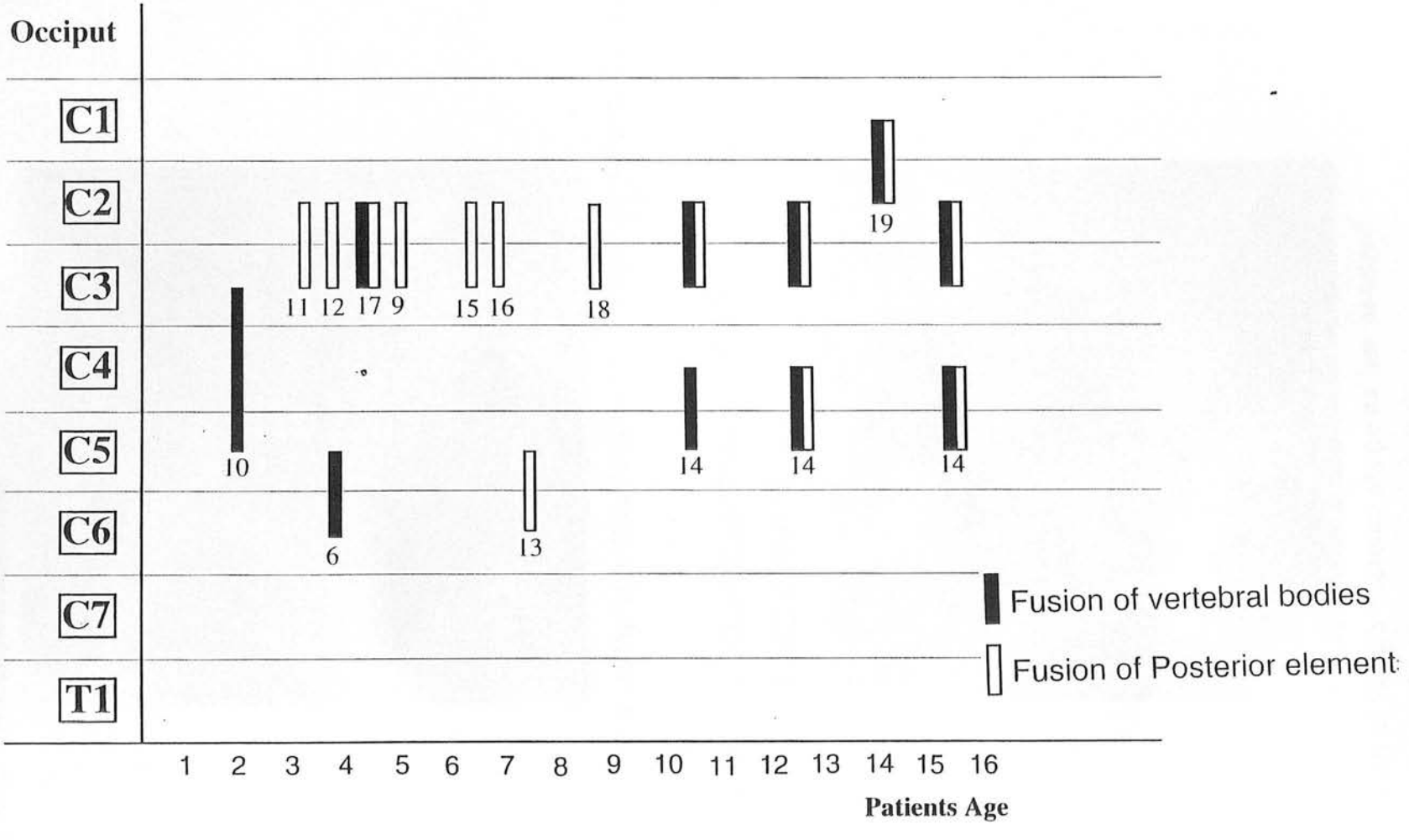
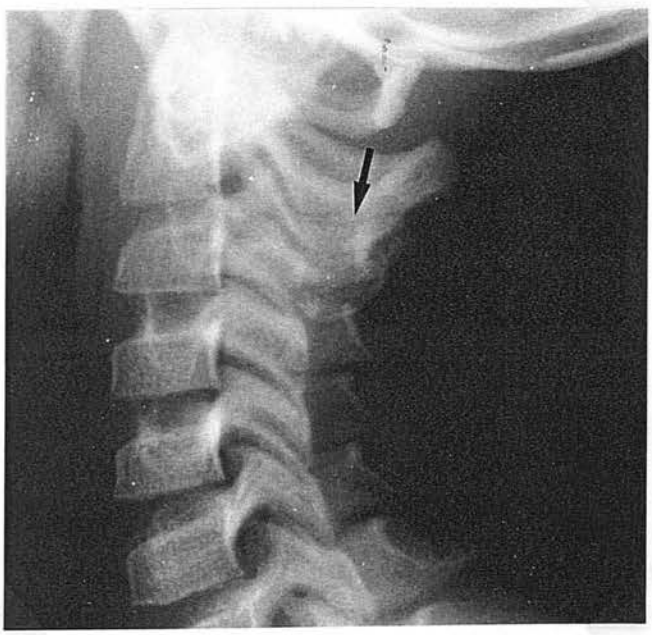


FIGURE 5.1 LEFT LATERAL CERVICAL SPINE RADIOGRAPH IN CASE 15 AT AGE THREE MONTHS

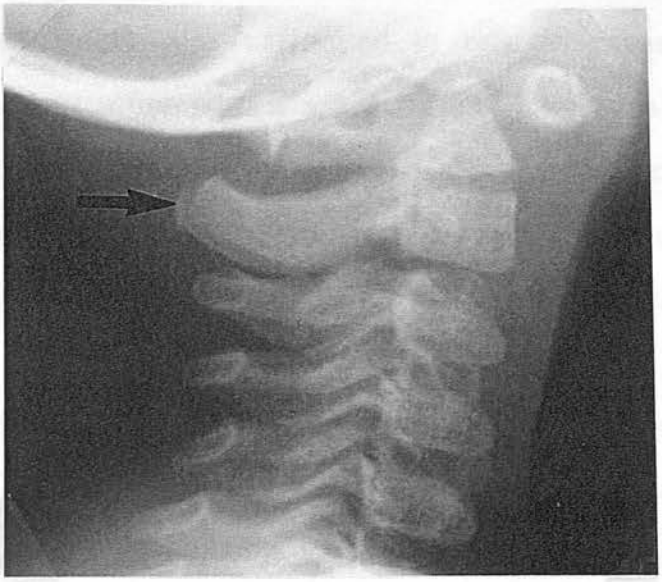
Left lateral radiograph demonstrating hypoplastic neural arch C1, but no fusions.

FIGURE 5.2. THE LEFT LATERAL CERVICAL SPINE RADIOGRAPH IN CASE 15 AT AGE SEVEN YEARS.



Fusion of C2/C3 Posterior elements has occurred.

FIGURE 5.3. THE RIGHT LATERAL CERVICAL SPINE RADIOGRAPH OF CASE 7 AT AGE FOURTEEN MONTHS.



Abnormally long spinous process of C2.

FIGURE 5.4 LEFT LATERAL CERVICAL SPINE RADIOGRAPH OF CASE 14 AGE 16 YEARS

Fusions affecting both vertebral bodies and posterior elements at both C2/C3 and C4/C5 levels.

THE HANDS

Clinical examination was performed in twenty cases. Incomplete, simple syndactyly affecting the second web space was found in four cases (no's 6,8,24 and 25). None of these cases had either undergone or were waiting for surgery to correct this, as the syndactylies did not interfere with hand function. No loss of function was detected in any other case.

Radiological examination of the hands had been undertaken in twenty two cases with sequential studies available in two cases. The time of the first radiograph ranged from three months to seventeen years, with a median age of seven years. Eight cases had no structural abnormality present. A wide range of symmetrical anomalies were detected in the remainder but no fusions were seen. The incidence of the different skeletal anomalies is shown in Table 5.3.

The commonest finding was that of anomalies affecting the epiphysis of the distal phalanx of the thumb. These epiphyseal anomalies took one of two forms: either the early appearance of the epiphysis in those under one year (it does not normally appear until eighteen months of age) or an unusually large epiphysis later in childhood. These are shown on serial radiographs of case 4 taken at four months and seven years in Figures 5.5 and 5.6.

The bone age was found to be delayed when compared to radiological standard radiographs (Greulich and Pyle, 1959). This was true for all cases where the epiphyses had not fused, although the amount of delay was variable. The exception was the single case who had completed

epiphyseal fusion, and was skeletally mature, The amount of delay in each case is shown in more detail in Table 5.4.

TABLE 5.3 ANOMALIES IN THE HANDS IN SAETHRE-CHOTZEN SYNDROME 22 cases, no asymmetrical anomalies.

Anomaly	No. of cases
THUMB	
Thumb distal phalanx large epiphysis	6
Thumb distal phalanx early epiphysis	2
FINGERS 2-5	
Distal phalanx hypoplastic	2
Distal phalanges Ivory epiphyses	1
Middle phalanx hypoplastic	2
Kirner's deformity	1
Clinodactyly	4
Camptodactyly	1
METACARPALS	
1st Pseudoepiphysis	4
2nd Pseudoepiphysis	2
3rd Peudoepiphysis	1
5th Pseudoepiphysis	1
Long metacarpals	1
RADIUS	
Radial head flattened	4

TABLE 5.4 COMPARISON BETWEEN THE CHRONOLOGICAL AGE AND THE BONE AGE IN THE HANDS OF CASES OF SAETHRE-CHOTZEN SYNDROME.

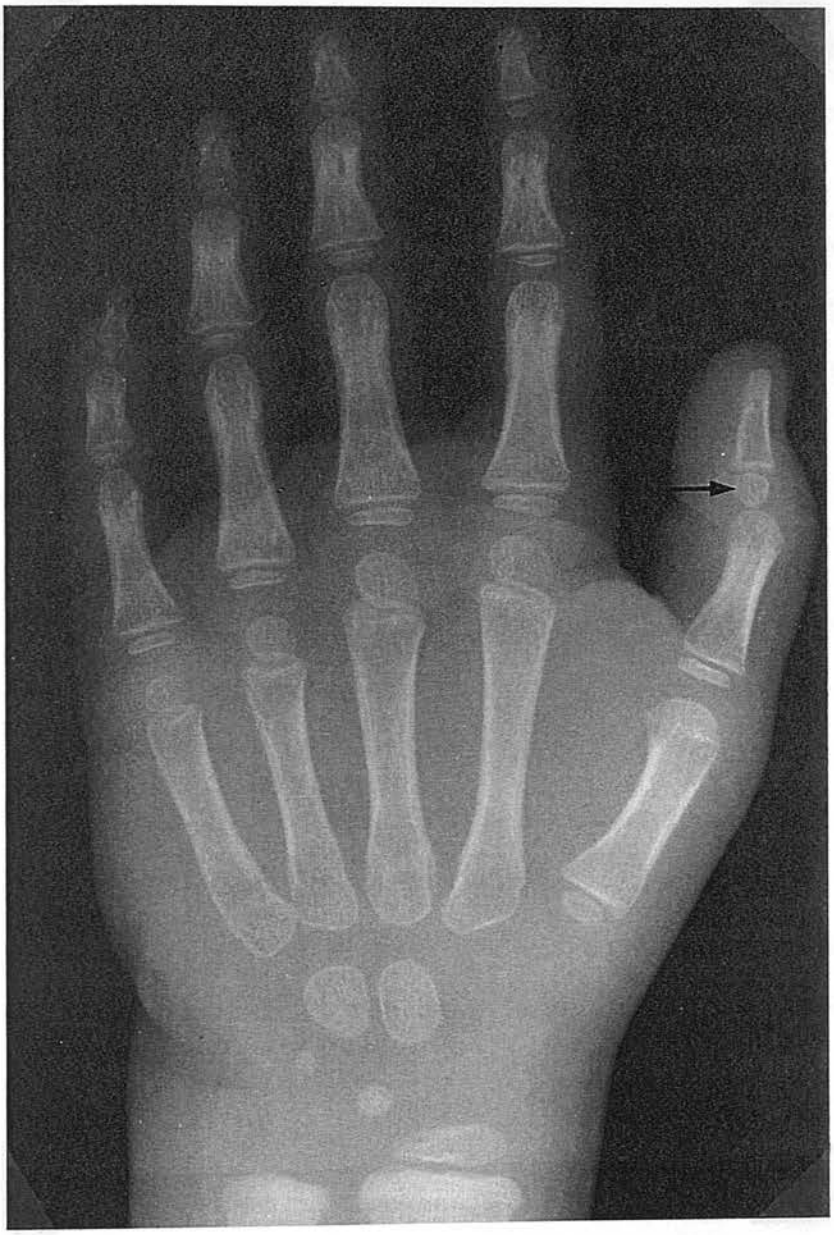
22 cases.

Case number	Chronological age (years)	Bone age (years)	Delay (years)
2.	4.5	2.0	2.5
	6.5	3.0	3.5
4.	0.5	Newborn	0.5
	7.0	5.0	2.0
6.	2.25	1.25	1.0
7.	4.25	3.5	0.75
8.	4.5	4.0	0.5
9.	6.0	5.0	1.0
10.	1.25	0.75	0.5
11.	4.0	3.0	1.0
12.	4.0	2.75	1.25
13.	8.5	7.0	1.5
14.	17.0	17.0	None
15.	7.5	5.5	2.0
16.	7.0	4.5	2.5
17.	4.25	3.5	0.75
18.	10	9.5	0.5
19.	13	11.75	1.25
21.	1.0	0.5	0.5
22.	1.0	0.5	0.5
23.	1.0	0.75	0.25
26.	9.0	6.75	2.25
28.	5.0	4.0	1.0
29.	2.5	2.0	0.5

FIGURE 5.5 RADIOGRAPH OF THE HAND OF CASE 4 AT FOUR MONTHS

Early appearance of the epiphysis of the distal phalanx of the thumb.

FIGURE 5.6. RADIOGRAPH OF THE HAND OF CASE 4 AT SEVEN YEARS



Large epiphysis of the distal phalanx of the thumb.

Note the pseudoepiphysis at the distal end of the first metacarpal.

Bone age five years (Greulich and Pyle, 1959), two years delayed.

THE FEET

Clinical examination of the feet was unremarkable apart from two cases (no's 8 and 25) who had incomplete, simple syndactyly of the 2nd web space. All cases were able to wear normal footwear without any difficulty and they had started walking by fourteen months of age (apart from case 2 who had talipes equinovarus).

Radiological examination of the feet was performed in twelve cases, and in a single case sequential studies were available. The age at the time of the radiograph ranged from three months to ten years, with a median age of four years. A range of minor anomalies were detected but these did not include any fusions and are shown in Table 5.5. All anomalies were symmetrical.

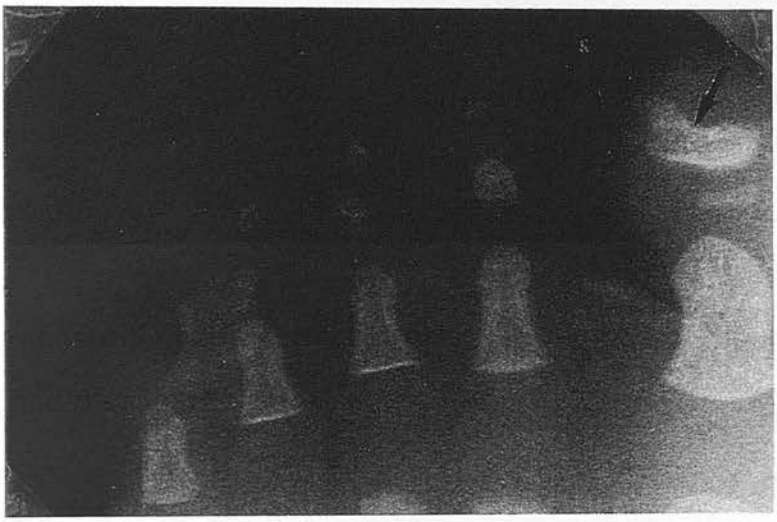
The toes were the only site affected, with no anomalies of the metatarsals or tarsals. Hypoplasia of the middle phalanx of toes 2-5 was the most common finding with 10/12 cases demonstrating this anomaly. All cases with abnormally broad phalanges of the hallux had both proximal and distal phalanges similarly affected. There was a single case of bifid terminal phalanx that could represent an attempt at duplication, see Figure 5.7., consistent with a diagnosis of Robinow-Sorauf syndrome.

TABLE 5.5. ANOMALIES OF THE FEET

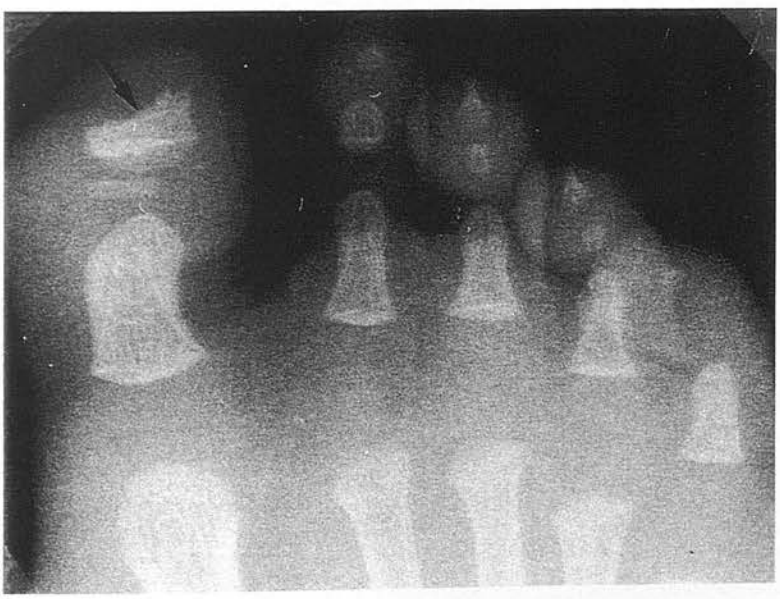
12 cases, 2 normal. None asymmetrical.

Site	No. of Cases
HALLUX	
Attempted duplication distal phalanx	1
Broad Distal phalanx	5
Broad Proximal phalanx	5
TOES 2- 5	
Hypoplastic terminal phalanx	9
Hypoplastic middle phalanx	10
Cone epiphysis proximal phalanx	1
Toe 2, Broad terminal phalanx	1
Toe 5, Fusion proximal and middle phalanges	1

FIGURE 5.7. RADIOGRAPHS OF THE FEET IN CASE 7 AGE FOURTEEN MONTHS.



Left demonstrating bifid terminal phalanx of the hallux, and hypoplastic middle and distal phalanges.



Right demonstrating symmetrical anomalies to the Left.
The attempt at duplication is consistent with a diagnosis of Robinow-Sorauf syndrome.

OTHER SITES

Clinical examination of other joints was concentrated on the elbows, shoulders and knees. All were unremarkable. Twelve cases underwent radiographic examination of other parts of the skeleton.

Eight elbow examinations were all normal with specifically no evidence of radio-ulnar synostosis. The three shoulder examinations likewise were normal. The full spine radiographs in both cases were taken a few months after birth as part of a skeletal survey and were normal. The hips and pelvis examination were both undertaken to investigate pain localised to the hip, but in both cases the radiographs were normal. The knees were radiographed following a history of trauma and also were normal. One ankle was radiographed for investigation of tallipes equinovarus (case 2). One other case underwent radiography of the ankle following trauma, and was unremarkable.

Ultrasound examination of the abdomen had been undertaken in case 16 to investigate the genitourinary system. This was normal. Echocardiography had been performed on case 8 to investigate a pansystolic heart murmur, and a small ventricular septal defect diagnosed.

DISCUSSION

CLINICAL EXAMINATION.

The absence of abnormal clinical findings and the unremarkable height and weight measurements suggests that the effects on the extracranial structures are at worst only minimal. There have been reports of abnormalites of stature (Pantke *et al.,* 1975; Freidman *et al.,* 1977) but there is no evidence to support this in this population. These results may reflect the observation that some with the condition may appear to be completely normal (Reardon and Winter, 1994).

THE CERVICAL SPINE

The presence of radiological anomalies of the cervical spine in 14/29 cases, is much higher than the incidence in the normal population, which has been reported as 0.5-3% (Shands and Bundens, 1956; Gray *et al.,* 1964). This finding is true both of congenital anomalies occuring in 7/29 cases and fusions occuring in 12/29 cases.

The presence of cervical fusions in this condition, at the C2/C3 level, has previously been reported as an isolated case (Pantke *et al.,* 1975). A later investigation into the cervical spine in this condition found no fusions, but this was also just a single case (Hemmer *et al.,* 1987). However, the incidence of fusions in this population (41%), compared with the normal population and the single previous report, is surprisingly high. Given that this population is still maturing and further fusions may develop, then even this may under estimate the incidence in the adult population.

It is interesting that most of the fusions affected the C2/C3 level, as this level has been reported to be most commonly affected in the normal population as well as in Crouzon and Pfeiffer syndromes (Brown *et al.,* 1964; Kreiborg, 1981; Moore *et al.,* 1995). However, unlike the two other complex craniosynostosis syndromes only two cases had more than a single level affected by fusion.

Progression of cervical fusions in this syndrome has not previously been reported. However, the sequential studies provide direct evidence for progression of the fusions in 8/10 cases. There is also indirect evidence to support progression with only 1/23 radiographs of those aged below two years having evidence of fusion, compared with 14/19 radiographs who had fusion who were greater than two years.

The pattern of fusions are interesting with the posterior elements affected more frequently at the C2/C3 level than the vertebral bodies. It will require subsequent studies to establish whether the fusion will progress to involve the vertebral bodies.

It is curious that in one example (case 14) evidence of progressive fusion between the ages of ten and thirteen years had no further radiographic changes at sixteen years. This too will require further sequential studies to determine whether this represents arrest of the fusion process, and to see whether this phenomonen is repeated, as other cases reach skeletal maturity.

THE HANDS

Radiographic examination of the hands has revealed a variety of anomalies, the distribution of these being more extensive than previous

reports, with thumb and finger phalanges affected as well as the metacarpals and the radius. Anomalies other than delayed bone age were present in 14/22 cases. The most consistent site for anatomical anomaly was the epiphysis of the distal phalanx of the thumb which has not been previously recognised. This epiphysis both appeared earlier in the young cases than is normal (Greulich and Pyle, 1959) and was abnormally large in a further six cases in older children.

Previous studies of the hands in this condition have emphasized brachydactyly as the major feature (Cohen, 1986) and the incomplete syndactyly affecting the second web space (Reardon and Winter, 1994). Other features observed included: clinodactyly, hypoplastic distal phalanges, finger like thumbs and differences in skin crease patterns (Pantke *et al.,* 1975; Freidman *et al.,*1977; Cohen, 1986). Metacarpal anomalies that have previously been reported include hypoplasia of the fourth metacarpals (Aase and Smith, 1970) and abnormal metacarpophalangeal profile pattern (Escobar and Bixler, 1977).

This new finding of anomalies of the epiphysis of the distal phalanx of the thumb in 8/22 case contrasts with the finding of 2/22 cases exhibiting hypoplasia of the middle phalanges, and 2/22 cases having hypoplastic distal phalanges (case 22 exhibiting both of these). Incomplete syndactyly of the second web space was seen in just 4/29 cases, no other web spaces were affected. This low incidence of brachydactyly and syndactyly in this population is surprising given that they have been described as characteristic features of the condition (Pantke *et al.,* 1975; Cohen 1986; Gorlin *et al.,* 1990; Shalin *et al.,* 1993).

The presence of this clinodactyly in 4/22 cases is unusual but needs caution in interpretation, because this is a small series and clinodactyly is not uncommon in a caucasian population, the incidence of which has been estimated to be between 0.1 and 1.0% (Poznanski, 1972). However, clinodactyly associated with Saethre-Chotzen syndrome has been reported previously in several cases (Saethre, 1931; Freidman *et al.,* 1977; Shalin *et al.,* 1993). Altogether these findings tentatively suggest that there may be a true association between these two conditions.

The single case of camptodactyly is notable since this does not appear to have been previously reported in association with Saethre-Chotzen syndrome. It occurs in less than 1% of the general population and too can be transmitted as an isolated finding in an autosomal dominant manner. The significance is unclear but the development of camptodactyly has been reported to be related to the development of clinodactyly (Poznanski, 1972).

The case of Kirner's deformity is particularly interesting because this deformity (which results from deflection of the distal phalanx in a volar direction at the epiphysis) is rare, having a reported incidence in the general population of just of 0.15% (Sugiura *et al.,*1961). This too has not been reported previously in association with Saethre-Chotzen syndrome.

Metacarpal anomalies of pseudoepiphyses, particularly affecting the first metacarpal is a new finding. However, the significance of finding pseudoepiphyses in the metacarpals should be treated cautiously as they commonly occur in normal populations, as well as being a feature of other conditions including Kniest disease (Poznanski, 1972). The

flattening of the radial head in 4/22 cases although mild has not been previously reported.

However, all cases with epiphyses present showed variable delay in the bone age when compared to normal individuals. This has not been previously reported. This may have clinical implications as for the timing of any surgery that requires illiac bone grafts which may need to be delayed to await skeletal maturity. The finding of differences in bone age between the carpal bones and the phalanges in 4/22 cases is curious, but the significance is unclear.

In conclusion a wider range of often rather subtle bone anomalies have been demonstrated in the hands than previously reported. The epiphyses appear to be primarily affected with the distal phalanx of the thumb appearing to particularly so. It is notable that no bone fusions were seen (unlike the hands of cases of the other craniosynostosis syndromes). The significance of all these anomalies is unclear but suggests that the expression of the mutant gene is more widespread in the hands than is currently thought.

THE FEET

The radiographs of the feet all showed at least one minor radiographic anomaly, in the twelve cases undergoing radiological examination.

A range of anomalies were seen. Hypoplasia of the middle phalanges was the most common, with 10/12 cases affected. The finding of broad phalanges has been noted previously (Saethre, 1931, Pantke *et al.,* 1975, Freidman *et al.,*1977) and is notable since this is a diagnostic feature of Pfeiffer syndrome (Gorlin *et al.,* 1990). The incomplete

syndactyly in 2/29 cases is an uncommon feature but too has been reported (Saethre, 1931; Chotzen 1932; Bartosocas *et al.,* 1970).

A particularly interesting anomaly was that of the bifid terminal phalanges (and may represent an attempt at duplication) of the great toes in case 7, see Figure 5.7. Although this anomaly has been previously described in Saethre-Chotzen syndrome (Kopysc *et al.,* 1980; Young and Harper, 1982), it had also been suggested that there was a subgroup with this anomaly (along with features of Saethre-Chotzen syndrome) who represented a separate distinct syndrome, and the name Robinow-Sorauf syndrome was proposed (Carter *et al.,* 1982). However, it has been clearly demonstrated by family studies this is not a separate entity but that the bifid terminal phalanx just one variable feature of a Saethre-Chotzen syndrome (Reid et al, 1993; Shidayama et al, 1995).

Finally, the clustering of anomalies within the phalanges of the toes with no anomalies in the metatarsals and tarsals is in contrast to the widespread anomalies detected in the hands. The reason for this paradox is unclear.

THE REMAINING SKELETON

No changes in the rest of the skeleton could be found. Specifically, there are no cases of radio-ulnar synostosis in this series which have been reported (Bartosocas *et al.,* 1970). The elbow radiographs were taken prospectively in eight cases but all were normal. These eight cases were those with evidence of extracranial manifestations of the condition and included four cases who had both cervical spine and

hands or feet anomalies (cases 6,11,12 and 19), while the other four cases had hand or feet anomalies (cases 4,21,22 and 28). It would seem then the incidence of radio-ulnar synostosis must be either exceptionally rare, occur after childhood or perhaps the report is based on an incorrect diagnosis of another craniosynostosis syndrome, perhaps an atypical Crouzon or Pfeiffer phenotype.

The clavicles and pelvis have previously been reported to demonstrate anomalies (Freidman *et al.,* 1977). However, none of the small number of cases investigated demonstrated these. This could be due to several reasons; firstly the rarity of the anomaly and the small numbers investigated, or secondly in this paediatric population any anomalies at these sites may not have developed yet.

THE VISCERA

Clinical examination and review of the case notes revealed few anomalies. These included hypospadias (case 19), Talipes equinovarus (case 2), Ventricular septal defect (case 8), congenital inguinal hernia (case 8). The association of the syndrome with genitourinary anomalies has been reported (Bartosocas *et al.,* 1970), but these were restricted to renal anomalies and cryptorchidism, rather than the genitourinary anomalies in these cases. The association of the syndrome with congenital heart defect has been made previously (Aase and Smith, 1970), but the single case here with a common anomaly is unlikely to be significant.

These results suggest that there is little evidence that these anomalies, which are common in the general population, are any more than isolated findings. However, there is a reported association between cervical

spine anomalies and genitourinary malformation (Hensinger, 1990), and both cases with genitourinary anomalies demonstrated this. Case 19 had both a cervical fusion and case 8 had an associated hypoplastic neural arch at C1.

CONCLUSIONS

It must be remembered when considering the results of this study that this population was selectively drawn from those with Saethre-Chotzen syndrome who exhibited craniofacial manifestations severe enough to warrant craniofacial management, rather than from all of those with this syndrome. This may account in part for both the high incidence and the range of anomalies seen within this population in comparison with previous reports. This population also has an unusual female to male ratio of 2:1, as generally the sexes are usually equally affected (Gorlin *et al.,*1990). However, it is difficult to explain any of these new findings due to this difference.

The results of the cervical spine study demonstrates that fusions can occur postnatally and are often progressive in nature. The finding that usually only single levels are affected within an individual differs from the other craniosynostosis syndromes who often have anomalies at multiple levels. The finding of a hypoplastic neural arch at C1 on the cervical spine radiograph is a good predictor of subsequent fusion, if this has not already occurred.

This finding of fusions has not been observed at other sites of the extracranial skeleton. This is in marked contrast to the craniosynostosis syndromes resulting from fibroblastic growth factor mutations. There

are however, anomalies often affecting the epiphyses and occurring on occasion throughout the bones of the hands, but restricted to the phalanges of the feet. The reason as to why this bizarre pattern of anomalies should occur is unclear.

The results of these investigations of those with Saethre-Chotzen syndrome contrast with previous reports of synostosis of the elbows (Bartosocas *et al.,* 1970), or anomalies of the pelvis and clavicles (Freidman *et al.,* 1977). This suggests that anomalies at these sites must be rare associations, if they are true associations at all, rather than isolated findings.

Overall these findings fail to support the hypothesis that the condition is a generalised skeletal morphogenesis in which craniosynostosis sometimes occurs (Freidman *et al.,* 1977). However, there do appear to be characteristic skeletal changes which often appear to be related to the epiphyses, and these have been demonstrated to be more widespread than in many of the previous reports.

CHAPTER SIX

CHAPTER SIX

FINAL DISCUSSION AND CONCLUSIONS

All four syndromes examined in this study, show a much wider range of anomalies than previously reported. Examination of patients, particularly with Apert syndrome, has confirmed that skeletal anomalies can be widely distributed. The results of the investigations, into each component of the skeleton, will be considered together.

THE CERVICAL SPINE

The association between craniofacial deformity and cervical spine anomaly is not unique to the craniosynostosis syndromes. Spinal fusions, hemivertebrae, and cervical spina bifida also occur commonly in hemifacial microsomia and Goldenhar syndrome (Sherk *et al.,* 1982). It is also reported that there is an increased frequency of cervical fusions in patients with cleft lip and palate, compared to the normal population (Sandham, 1987). It has been proposed that this relationship is predictable because of the close spatial relationship between sclerotomic derivatives of the cervical somites and the branchial arches, and the similar time course over which segmentation and branchial arch differentiation occurs (Sherk *et al.,* 1982).

Several findings are common to all four syndromes investigated. The clear demonstration of cervical spine fusions in all of these syndromes is at a higher incidence (Table 6.1), than in the general

TABLE 6.1 COMPARISON OF THE CERVICAL SPINE ANOMALIES

	Congenital Anomalies	Fusion Incidence	Fusion Level
Crouzon	Butterfly vertebrae, Hypoplastic body, Enlarged neural arch.	20%	C2/C3 C5/C6
Pfeiffer	Hypoplastic neural arch C1, Butterfly vertebrae, Hemivertebrae.	70%	C2/C3
Apert	Enlarged dens	63%	C5/C6
Saethre - Chotzen	Hypoplastic neural arch C1, Enlarged spinous process C2.	41%	C2/C3

population which ranges from 0.5 - 5% (Shands and Bundens, 1956; Gray *et al.,* 1964; Brown *et al.,* 1964). Comparison of the results of this study with previous reports shows that Crouzon syndrome has a lower incidence, and Pfeiffer syndrome a higher incidence, of fusions. This combination may be due in part to the method of selecting our populations and hence the inclusion of atypical Pfeiffer phenotypes in their correct syndrome group rather than as cases of Crouzon syndrome. The incidence of fusions in Apert syndrome is similar to previous reports (Hemmer *et al.,* 1987; Kreiborg *et al.,* 1992). In marked contrast there is no previously published series of cervical spine anomalies in Saethre-Chotzen syndrome.

There is also good evidence from the results of the serial radiographic studies that the fusions of the cervical spine can be progressive in all four syndromes.

However, the four syndromes considered here also display differences both in the type and position of anomalies within the cervical spine (see Table 6.1), although the anomalies present within each syndrome are not constant.

The level of fusions most frequently involved in each syndrome is variable. For Pfeiffer and Saethre-Chotzen syndromes C2/3 is most frequently involved, whereas in Apert syndrome it is C5/6. However, in Crouzon syndrome C2/3 and C5/6 are almost equally affected. The levels affected are the same as the most commonly affected sites in the general population. In a series of 1400 "skeletonised" cervical spines, where cervical fusion was shown to occur, the C2/3 level was the most commonly affected level (39% of cases), with

C5/6 the next most commonly affected level (28% of cases) (Brown *et al.,* 1964).

The levels of fusion in Crouzon syndrome in this series, where both C2/3 and C5/6 were similarly affected, differs from all previous reports which had demonstrated that C2/3 was clearly the most commonly affected level, and C5/6 only reported as being occasionally affected (Kreiborg, 1981; Hemmer *et al.,* 1987; Proudman *et al.,* 1994). This may be due to the fact that this study used sets of cervical spine films rather than cephalograms to examine the cervical spine. Cephalograms do not always include the lower cervical spine, and so C5/C6 fusions may have missed.

Progressive fusion of the spinal vertebrae is also a feature of an unrelated condition, Fibrodysplasia ossificans progressiva (Wynne-Davis *et al.,* 1985), and although the diagnosis can be made clinically it is notable that progressive fusions of the cervical spine are not peculiar to these (or other) craniosynostosis syndromes.

The presence of congenital malformations (other than fusions) varies in the four syndromes studied. The presence of congenital "Butterfly" vertebrae is almost exclusive to Crouzon syndrome. These have been reported as occurring most commonly in the lumbar region in the general population (Muller *et al.,*1986). In an earlier study of syndromic craniosynostoses, "Butterfly" vertebrae were found exclusively in Crouzon syndrome, with an incidence of 12% (Hemmer *et al.,* 1987), which is the same as the incidence of occurence reported in this study (Chapter Two). The association of

"Butterfly" vertebrae and the development of subsequent fusions, albeit occasionally at different levels is quite curious, but the mechanism may involve deficiencies of disc material (Muller *et al.,*1986). However, the finding of a "Butterfly" vertebra on cervical spine radiographs, may be used as a marker of an increased chance of developing subsequent fusion. The two examples of "Butterfly" vertebrae seen in Pfeiffer syndrome were both associated with cervical fusions. This has not been previously reported, but may reflect the higher incidence of fusions in the Pfeiffer syndrome patients.

The development of a "Butterfly" vertebra can occur between three and six weeks of intrauterine life. However, as there are several developmental mechanisms which can result in this anomaly, the exact embryological time that it is produced is uncertain (Muller *et al.,* 1986). It is noteworthy that this period of embryological life can overlap with the timing of syndactyly production (see below -The Hands). The mechanism by which these malformations are produced is unclear but it has been suggested that it may involve anomalies of the notocord (Kjaer *et al.,* 1994).

The presence of a hypoplastic neural arch involving C1 appears to be associated with the development of fusions in both Pfeiffer syndrome and Saethre-Chotzen syndrome. This is curious given the different genetic mechanisms which give rise to these syndromes. Thus the presence of a hypoplastic neural arch involving C1 on a cervical spine radiograph of a child with either of these conditions may be a guide to the likelihood of subsequently developing fusions.

The absence of malformations, other than the enlarged odontoid peg in Apert syndrome is similar to the findings of Ferraro (1991). The finding of a large odontoid peg has not been reported in either Crouzon, Pfeiffer or Saethre-Chotzen syndromes. However, an enlarged odontoid peg has been previously noted in Carpenter's syndrome which is an autosomal recessive craniosynostosis syndrome (Hemmer *et al.*, 1987). The significance of this finding in cases of both Apert and Carpenter's syndromes is unclear.

The clinical significance of these fusions with their progressive nature is uncertain. No patient reported any neck symptoms and clinical examination revealed no obvious loss of neck movements or neurological deficit. However, spontaneous hemiplegia in a twelve year old boy with Crouzon syndrome with cervical spine fusions has been reported (Proudman *et al.,* 1994). Although the hemiplegia resolved, he died six years later and was found at autopsy to have acute compression of the cervical cord. It has also been reported that in patients with Apert syndrome, C1-C2 can undergo subluxation, with potentially lethal consequences (Ferraro, 1991).

Congenital fusion of the cervical spine has been associated with clinical sequelae in other conditions (Klippel and Feil, 1912). Currently, the term Klippel-Feil syndrome applies to congenital cervical spine fusion from two segments to entire spine fusion, with the exception of anomalies of the occipito-cervical junction, atlanto-occipital fusion, basilar impression and odontoid anomalies which are considered separate entities (Hensinger, 1990). The condition is due to failure of segmentation of cervical somites *in utero* and is associated with a high incidence of genitourinary, cardiovascular and

neurological abnormalites (Hensinger, 1990). Klippel-Feil cases are reported to have limited neck motion, although this is not detectable if less than three segments are involved (Gray *et al.,* 1964). It is notable that the findings in this study of those with block vertebrae (Pfeiffer syndrome and a single case of Crouzon syndrome) contrast to this earlier report, as none of these patients had discernable limitation of movement, despite some patients having more than three adjacent levels affected.

Although it has been stated that there are no symptoms directly attributable to the fused cervical vertebrae, it is recognised that hypermobility of the spine occurs at adjacent levels to the fused levels. Because of the increased demands on these joints it has been suggested that early degenerative arthritis may occur. This may in turn, produce mechanical symptoms due to joint irritation, or neural symptoms due either to root irritation or spinal cord compression (Hensinger, 1990). Those with short segment fusion will have more joints to compensate, and fusions of the lower cervical spine are more easily compensated by the upper cervical spine where greater joint movement occurs.

In Klippel-Feil syndrome it is recognised that neurological symptoms are rare before twenty years of age. As the patients included in this study were below this age, if neurological signs are to be produced by the same mechanism in Klippel-Feil syndrome, they may not have had time to manifest themselves. This suggests that these cases need careful long term follow up in adulthood.

Occipitalisation of C1 (or occipito-cervical synostosis), was demonstrated in one case. This occurred in a boy with Pfeiffer

syndrome aged five years, who had severe cranial and extracranial manifestations of the condition (case 14, Chapter Three). This was his only cervical fusion on three serial radiographs from six months to five years. This radiological finding is important because 50% of cases with this anomaly are reported to develop atlanto-occipital instability (von Torklus and Gehle, 1972). This may also produce occipital pain, vertigo and unsteady gait, although often not until the fifth decade of life (Hensinger, 1990).

Cervical fusions, particularly those affecting the higher levels, may also have important consequences for head posture and resulting influences on craniofacial growth and dental occlusion. It has been shown in those who undergo elective cervical spine fusion that head posture is altered in comparison to controls (Makofsky and Sexton, 1994). If altered head posture does occur then there are profound implications for an affected individual relating to facial growth and upper airway obstruction. Head posture is due in part to the morphology of both the individual components and the overall shape of the cervical column, especially the first cervical vertebra. Consequently, cervical spine anomalies may alter head posture (Kylamarkula and Huggare, 1985; Hellsing *et al.,* 1987; Solow and Siersbaek-Nielsen, 1992). The posture is related to the craniocervical angle, and it has been well recognised that this affects facial growth (Solow and Kreiborg, 1977). More recently, cephalometric studies have confirmed that a large craniocervical angle, produced by an upright cervical column, will result in backward displacement of the temporomandibular joints and hence produce a reduction in the horizontal component of facial growth of the maxilla (Solow and

Siersbaek-Nielsen, 1992). Conversely, a small craniocervical angle has been shown by cephalometric analysis to produce a reduction in the vertical growth of the face. It has also been shown that mandibular growth can be directly correlated to growth of individual vertebrae, and that vertebral dimensions can be used to predict mandibular growth (Huggare and Cooke, 1994; Nevard, 1994). However, these findings have all been performed on populations which do not include those with complex craniosynostosis syndromes, so care has to taken when assessing their significance. However, fusion of the odontoid peg and the C1 has been observed in Saethre-Chotzen syndrome (case 19, Chapter Five), and this may directly affect head posture.

Head posture and the presence of upper airways disease or obstruction are also interelated (Linder-Aronson, 1979; Wenzel *et al.,*1985; Moore, 1993). This is interesting because upper airways obstruction is commonly found in those with severe maxillary hypoplasia as a manifestation of the craniosynostosis syndromes of Crouzon, Pfeiffer and Apert (Lauritzen *et al.,* 1986; Mixter *et al.,* 1990; Moore, 1993). The finding of upper airway obstruction in these three syndromes, despite differences between the incidence and levels of cervical fusion, suggests that this is due primarily to the effects of the craniosynostosis on the craniofacial skeleton. However, severe cases of all three syndromes, who have restricted facial growth could then have secondary effects both on upper airway obstruction and further facial development by alterations in head posture due to any cervical fusions. Relieving upper airway obstruction in non-syndromic individuals does alter head posture, and

leads to alterations in mandibular growth (Linder-Aronson *et al.,* 1986). Thus by using serial cephalograms in severely affected individuals who undergo tonsillectomy, adenoidectomy or craniofacial surgery to correct maxillary hypoplasia, it would be possible to detect any alterations in head posture produced. Similarly, in those cases with severe maxillary hypoplasia who require long term C.P.A.P. therapy, it would be worthwhile investigating whether their head posture changes as a result of therapy.

Head posture in infants has been shown to be important in the establishment of the intracerebral venous drainage (Hakim, 1985). The presence of cervical fusions at a few months of age has been demonstrated in Pfeiffer syndrome (Moore *et al.,* 1995). Anomalous venous drainage of the intracerebral circulation occurring via a transosseous pathway to connect with the external jugular and vertebral systems is known to have occurred in a Pfeiffer syndrome case with the severe craniofacial manifestation of a clover leaf skull (case 1, Chapter Three). Division of these vessels when aged seven years resulted in intraoperative death. The cervical spine in this case clearly demonstrated multiple fusions shortly after birth (see Chapter Three), and this suggests that posture may have influenced the development of this anomalous drainage in this case. The clinical significances of this are clearly important and have been reported (Anderson *et al.,* 1996b).

Finally, when considering the results of the investigations into Apert, Pfeiffer and Crouzon syndromes, it is unclear why the three syndromes, which can all result from a mutation of the FGFR 2 gene, should result in wide differences in phenotypic presentation within

the cervical spine in terms of the incidence and type of congenital malformations and the incidence, patterns and frequency of fusions.

In conclusion the cervical spine in all four syndromes studied is affected by congenital malformations and by an increase in the incidence of vertebral fusions in comparison to the normal population. These fusions are often progressive throughout childhood. However, there are marked differences between the syndromes in both the nature and position of these congenital anomalies and the cervical fusions. No symptoms were recorded in this series, and the clinical examination was universally unremarkable. However, there is some evidence that there are possible clinical sequelae resulting from the development of fusions. These relate to facial growth during childhood and neurological symptoms in adulthood.

THE THORACIC, LUMBAR, SACRAL AND COCCYGEAL SPINE

The lumbar and thoracic spine was examined in a small number of cases of Crouzon and Saethre-Chotzen syndrome, but not in any cases of Pfeiffer or Apert syndrome. The finding of a "Butterfly" vertebra in the thoracic region of a case of Crouzon syndrome is interesting. These have been reported as occurring most commonly in the lumbar region in the general population (Muller *et al.*,1986). When these occurred in the cervical vertebrae both in Crouzon and the two cases of Pfeiffer syndrome, fusion of the cervical vertebrae was seen on subsequent radiographs. It has been observed that

there is a deficiency of disc material associated with "Butterfly" vertebrae, and this may predispose such an anomaly to subsequent fusion with adjacent vertebrae (Muller *et al.,* 1986). Serial radiographs are planned as part of long term follow up to investigate whether fusions develop in the thoracic spine, but it is notable that this case is already aged seventeen years and currently has no fusions affecting the cervical spine. Anomalies affecting the spine outside the cervical region in Crouzon syndrome are exceptional, with a single case of sacrococcygeal protruberance (Sagehashi 1992).

Lumbar spina bifida and sacrococcygeal protruberance have been previously reported in Pfeiffer syndrome (Moore *et al.,* 1995), and sacrococcygeal protruberance reported in a possible case of Apert syndrome (Wells *et al.,* 1990). A single case of a hemivertebra in the lumbar spine in a case of Apert syndrome has been observed (Cohen and Kreiborg, 1993c), but no cases of "Butterfly" vertebrae have been reported. This suggests that malformations of the lower spine are indeed rare in these syndromes. Fusions of the lumbar and thoracic spine have occasionally been reported in Apert syndrome (Rubin *et al.,* 1972; Musallam *et al.,* 1975; Cohen and Kreiborg, 1993c). None of the Pfeiffer or Apert syndrome cases underwent radiological evaluation of the lower spine, and there was no clinical evidence of anomalies, suggesting that any which do occur are either mild or rare. The lower spine radiographs of Saethre-Chotzen syndrome cases were also all unremarkable, and there are no previous reports of anomalies at these sites.

Although there was no evidence of vertebral fusions outside the cervical region, in any of the four syndromes studied, those patients undergoing radiological examination were all only a few months old, which may be important if fusions are progressive. Further study is required to ascertain the incidence and significance of anomalies in all four syndromes and to look for evidence of progressive fusion.

THE HANDS

All four syndromes exhibited anomalies and are shown Table 6.2.

Soft tissue anomaly in the form of syndactyly was seen universally in Apert syndrome and occasionally in Pfeiffer (3/21 cases) and Saethre-Chotzen (4/20) syndromes, but never in Crouzon syndrome. There have been previous reports of Crouzon syndrome with syndactyly affecting either the second or the third web spaces (Proudman *et al.,* 1994), but these only represent isolated cases. The rarity of syndactyly in Crouzon syndrome, raises doubts as to whether syndactyly is an extracranial manifestation of this condition or if it is present, (and it is a relatively common congenital anomaly), then the finding may be just coincidental.

Previous reports of syndactyly in Crouzon syndrome could represent atypical phenotypes of other syndromes, which have been shown to have often been incorrectly labelled as Crouzon syndrome (Anderson *et al.,* 1996a). Radiographic findings of the population in which syndactyly was described included hypoplasia of the middle phalanx of the little fingers (Proudman *et al.,* 1994). This is the commonest anomaly of the hands in Pfeiffer syndrome in the present study (see

TABLE 6.2 COMPARISON OF THE HAND ANOMALIES

	Common (>50% cases)	Uncommon (<50% cases)
Crouzon	None	Carpal fusions, Pseudoepiphysis 1st metacarpal.
Pfeiffer	Hypoplastic middle phalanx little finger.	Syndactyly, Broad thumb phalanges, "Angelwing" epiphysis of proximal phalanx, Hypoplastic middle and distal phalanges of Index finger, Metacarpal fusions, Carpal fusions.
Apert	Syndactyly Symphalangism, Metacarpal fusions, Carpal fusions.	None
Saethre-Chotzen	Delay in bone age (Greulich and Pyle, 1959)	Large epiphysis distal phalanx of thumb, Clinodactyly, Pseudoepiphyses of metacarpals.

Chapter Three). This casts doubts on the diagnosis of Crouzon syndrome in the previous report with syndactyly (Proudman *et al.,* 1994). The reported finding of syndactyly in Crouzon syndrome seems to be either very rare or spurious, but D.N.A. analysis may assist in clarifying this issue.

The position and extent of the cutaneous syndactyly in the Pfeiffer and Saethre-Chotzen syndrome cases was symmetrical. This did not apply to the Apert syndrome cases, which also involved lateral phalangeal fusions as part of the syndactyly, where asymmetry was observed in several cases. This finding in the Apert syndrome cases contrasts with previous extensive reviews of the hand anatomy in this condition, which found that the anomalies of the hands were symmetrical in all cases (Park and Powers, 1920; Upton, 1991). However, exceptions to this have recently been reported by Cohen and Kreiborg (1995), who have noted unilateral finger duplication. The three further cases of unilateral finger duplication presented in Chapter Four provide further evidence that anomalies of the hands may not always be symmetrical.

It is interesting to speculate why the three syndromes which can result from FGFR 2 mutations have such marked differences in the presence and extent of syndactyly, especially in Pfeiffer syndrome, where the severity of syndactyly ranged from complete to absent, and second, third and fourth webs were all on occasion affected. Syndactyly develops as a result of the failure of the normal process involved in hand formation, early in intrauterine life. The upper limb buds appear two days before the lower limb buds in the fourth week *in utero*. During the fifth week the digital rays develop following the

breakdown of the apical ectodermal ridge and the laying down of mesoderm (O'Rahilly and Gardner, 1975). The first process requires apoptosis of some cells of the apical ectodermal ridge for normal interdigital clefting or else syndactyly will result (O'Rahilly and Gardner, 1975). This mechanism would appear to be universally affected in Apert syndrome, while retaining the potential to be interfered with in Pfeiffer and Saethre-Chotzen syndromes, but never affected in Crouzon syndrome. As FGFR 2 is known to be expressed in the cells of the limb bud (Reardon and Winter, 1995; Wilkie *et al.,* 1995a), the finding of syndactyly in Apert and Pfeiffer syndrome is perhaps not surprising. What is unclear is why there is no syndactyly in Crouzon syndrome and, even more difficult to explain, is why there is syndactyly in Saethre-Chotzen syndrome in the presence of normal FGFR 2 receptors. Clearly, syndactyly can represent the same end result of different anomalies.

The anomalies of the bones seen included both morphological changes and fusions (apart from Saethre-Chotzen syndrome). The number of sites of morphological anomalies for Crouzon, Pfeiffer and Saethre-Chotzen syndromes was higher than previously reported (Proudman *et al.,* 1994; Saldino *et al.,* 1972; Pantke *et al.,* 1975).

The phalanges were affected in Pfeiffer, Apert and Saethre-Chotzen syndromes. These syndomes all had anomalies affecting the epiphyses, although not in the same manner. The "angelwing" epiphysis of the proximal phalanx of the thumb was only found in Pfeiffer syndrome. Pseudoepiphyses of the proximal phalanges were only seen in Apert syndrome, and the finding of enlarged epiphysis of the distal phalanx of the thumb was restricted to Saethre-Chotzen

syndrome. The middle phalanx was anomalous in both Apert and Pfeiffer syndromes, it being universally absent in Apert syndrome and commonly hypoplastic in Pfeiffer syndrome. The phalanges of the thumb in Pfeiffer and Apert syndrome were on occasion broad (but curiously not in Crouzon syndrome where this anomaly can affect the 1st ray in the feet, see Chapter Three). The finding of pseudoepiphyses occurring at the distal end of the proximal phalanges in Apert syndrome is of uncertain significance. Why this finding is limited to Apert syndrome, and whether this has any role in the subsequent process of symphalangism with the distal phalanx is unclear.

The metacarpals of all syndromes had examples of hypoplasia. The significance needs to be interpreted with caution as hypoplasia of the metacarpals are often seen in the normal population (Burke *et al.*, 1990). Pseudoepiphysis of the 1st metacarpal was seen in both Crouzon and Saethre-Chotzen syndomes. This anomaly has been investigated in detail in non-syndromic individuals, where it is due to changes in the structure of the underlying cartilage (Haines, 1974). The resulting radiographic anomaly is commonly seen in the normal population (Poznanski, 1972), and has been reported as occurring constantly without significance in longitudinal studies of the general population (Lee and Garn, 1967). Consequently, it may be that the absence of this finding in radiographs of Pfeiffer and Apert syndrome cases is more significant.

No morphological anomalies of the carpal bones in any of the syndromes, other than the universal delay in their develpoment in Saethre-Chotzen syndrome were observed. These results contrast

with the findings of bone development elsewhere. The bone development of the knee in infants with Pfeiffer syndrome was universally delayed, but development of the knees in a similar age group of Crouzon cases was normal (see Chapters Two and Three). The reason for the differences in bone age as determined by the carpal bones (Greulich and Pyle 1959), and the knee in Pfeiffer syndrome (Pyle and Hoerr 1969) is unclear and warrants further investigation.

Fusions affecting the phalanges were observed in Apert and (less commonly) in Pfeiffer syndrome, but not in Crouzon syndrome. The metacarpals, especially the fourth and fifth, were almost always fused in Apert syndrome, occasionally in Pfeiffer syndrome, but never in Crouzon syndome. However, fusion of the carpal bones was seen in all three syndromes, although they occurred more commonly in Apert syndrome.

Comparison of the pattern of anomalies for each syndrome suggests an increasing range of severity from the mildly affected or normal Crouzon syndrome, to the severely affected and always abnormal Apert syndrome, with Pfeiffer syndrome between these two extremes. There were no fusions seen in any cases of Saethre-Chotzen syndrome but there was the universal delay in bone age and pseudoepiphyses of the metacarpals, other than the first, which appears to be peculiar to this syndrome.

In conclusion a much wider range of anomalies of the hands have been observed for Crouzon, Pfeiffer and Saethre-Chotzen syndromes than previous reports suggested, and these anomalies occur with greater incidence in Crouzon and Saethre-Chotzen syndromes.

THE FEET

Anomalies were detected, on occasion, in the feet of patients from all four syndromes studied. However the feet of patients with Crouzon, Pfeiffer and Saethre-Chotzen syndromes (but never Apert syndrome), may occasionally be normal. The anomalies can produce both soft tissue and skeletal anomalies. The range of anomalies and their incidence has been summarised in Table 6.3.

Syndactyly was seen in both Pfeiffer (2/21) and Saethre-Chotzen (2/29) syndromes and was universally present in Apert syndrome. There were no examples of syndactyly in Crouzon syndrome. The syndactyly in both Pfeiffer and Saethre-Chotzen syndromes was symmetrical, but this was not always the case in Apert syndrome (however, there were 2 cases of Pfeiffer syndrome with skeletal asymmetrical skeletal anomalies). These findings are similar to the hands, and it is interesting to note that all those cases affected by syndactyly of the feet, regardless of syndrome, had associated syndactyly of the hands. This suggests that there is a common mechanism producing syndactyly (see The Hands, Chapter Six) to affect both the upper and the lower limb buds.

The new finding of asymmetrical anomalies in Apert syndrome contrasts to earlier studies which found that the anomalies of the feet were symmetrical in all cases (Park and Powers, 1920; Upton, 1991). The results of this investigation are perhaps not so surprising given that asymmetrical anomalies of the hands have been reported (Cohen and Kreiborg, 1995). The underlying mechanism responsible

TABLE 6.3 COMPARISON OF FOOT ANOMALIES

	Common (>50% cases)	Uncommon (<50% cases)
Crouzon	None	Broad 1st ray, Phalangeal fusions, Tarsal fusions.
Pfeiffer	Broad big toe phalanges, Hypoplastic middle phalanges toes 2-5,	Syndactyly, Broad 1st metatarsal, Phalangeal fusions, Metatarsal fusions, Tarsal fusions.
Apert	Syndactyly, Hypoplastic distal phalanges, Metatarsal fusions, Tarsal fusions.	Transverse fusions of phalanges, Os peroneum.
Saethre-Chotzen	Hypoplastic middle and distal phalanges.	Syndactyly, Broad big toe.

for this developmental anomaly is unresolved, but may involve local influences during foot formation in weeks five to six *in utero*.

The skeletal anomalies include morphological anomalies as well as fusions. The morphological anomalies of the phalanges included examples of a broad great toe in all syndrome types. This is important when it is recalled that the finding of a broad great toe is a classical feature of Pfeiffer syndrome and is used for clinical diagnosis (Gorlin *et al.*, 1990). Clearly the use of this feature on its own is unreliable in distinguishing between syndromes, although there can be no doubt that it is commonly found in Pfeiffer syndrome (11/21 cases).

The middle phalanx was (with two exceptions) absent in all toes in Apert syndrome, hypoplastic in 13/22 cases of Pfeiffer syndrome, hypoplastic in 10/12 cases of Saethre-Chotzen syndrome, and hypoplastic in 4/20 cases of Crouzon syndrome. In Saethre-Chotzen syndrome the distal phalanx was also frequently hypoplastic (9/12 cases). There were no anomalies outside the phalanges in the feet in Saethre-Chotzen syndrome, again suggesting that the mechanism producing the anomalies is different in this syndrome. In Apert syndrome, pseudoepiphyses occurring at the distal end of the proximal phalanges were a common finding. This is similar to the findings in the hands, and again these preceded the development of symphalangism, suggesting that they may play some role in that process.

The metatarsals were occasionally broad in Crouzon syndrome, but frequently broad in Pfeiffer and Apert syndromes. The first metatarsal was almost universally partially duplicated proximally in

Apert syndrome, and occasionally in Pfeiffer syndrome. Complete duplications of the first metatarsal were seen as symmetrical anomalies in cases of both Pfeiffer and Apert syndrome, this being a new finding for Apert syndrome. In Apert syndrome alone the 5th metatarsal was occasionally hypoplastic. There were no patterns of morphological anomalies of the tarsal bones in any syndrome, although an enlarged Os peroneum was found in the older cases of Apert syndrome.

Fusions were seen in Apert, Pfeiffer and Crouzon syndromes. No fusions were present in Saethre-Chotzen syndrome. The phalanges were affected most commonly in Apert syndrome, and also in Pfeiffer and Crouzon syndrome. The metatarsals were affected by fusions in Pfeiffer and Apert syndrome but not Crouzon syndrome. Fusions of the tarsals were observed in all three syndrome types, again Apert syndrome being the most severely affected.

The anomalies in Crouzon syndrome of broad phalanges and metatarsals, hypoplastic middle phalanges and phalangeal fusions are in marked contrast to the findings in the hands in which the comparable phalanges and metacarpals are all normal. It is interesting to speculate whether this is in part due to the delayed development of the lower limb bud, which is two days later than the upper limb bud (O'Rahilly and Gardner, 1975; Fitzgerald and Fitzgerald, 1994).

Comparison of the pattern of anomalies for each syndrome produces similar findings to the patterns in the hands suggesting an increasing range of severity for the three syndromes resulting from mutations of the FGFR 2 gene. This extends in broad terms from the mildly affected Crouzon syndrome, to the severely affected and

always abnormal Apert syndrome, again with Pfeiffer syndrome between these two extremes. The anomalies in Saethre-Chotzen syndrome have a different pattern, although hypoplasia of the middle phalanx is a common feature. Again this suggests that a different biochemical mechanism is responsible for the production of the anomalies in Saethre-Chotzen syndrome.

In conclusion a much wider range of anomalies have been described in the feet, in all of these syndromes, than existing reports suggest.

THE ELBOWS

The elbows demonstrated a range of both clinical and radiological anomalies in Crouzon, Pfeiffer and Apert syndromes. However, the elbows in Saethre-Chotzen syndrome cases were always normal. The radiological anomalies associated with each syndrome are summarised in Table 6.4.

Reduced movement of the elbow joint was observed in Crouzon, Pfeiffer and Apert syndromes. Clinically determined loss of movement in Crouzon syndrome was found in 5/44 cases (Chapter Two), which is similar to previous reports which identified an incidence of 16% - 18% (Kreiborg, 1981; Proudman *et al.,* 1994). The incidence of loss of movement was higher in Pfeiffer syndrome with 12/21 cases, which was surprising given that previously it had been reported that elbow anomalies rarely occur in Pfeiffer syndrome (Cohen, 1986; Gorlin *et al.,* 1990). However, reduced movement of the elbows was found in only 26/43 of Apert syndrome (Chapter Four), which had previously been reported to be almost universally

TABLE 6.4 COMPARISON OF ELBOW ANOMALIES

	Common (>50% cases)	Uncommon (<50% cases)
Crouzon	None.	Radial head subluxation Delayed radial head epiphysis, Synostosis.
Pfeiffer	Absent radial head epiphysis, Radial head subluxation or dislocation.	Humero-ulnar synostosis, Humero-radial synostosis, Delayed olecranon epiphysis. Radial head "mushrooming".
Apert	Radial head subluxation or dislocation.	Epiphyseal delay, Humero-ulnar synostosis, Radial head "mushrooming".
Saethre-Chotzen	None.	None.

present in adults (Cohen and Kreiborg, 1993c). This apparent difference could be explained by the fact that fusions can be progressive and that there is a difference in ages between the two populations studied. Overall, the incidence of reduced elbow movement is lowest in Crouzon syndrome and highest in Apert syndrome.

The radiological anomalies consisted of both morphological and fusion anomalies seen in all three syndromes. Anomalies were more common in Apert (25/36 cases) and Pfeiffer (11/16 cases) syndromes than Crouzon syndrome (8/22 cases). The relative incidence of anomalies in Crouzon syndrome could be even less than these figures suggest since the remaining cases of Crouzon syndrome have not undergone radiographic examination, and they were clinically normal. The apparently relatively lower incidence of anomalies in Apert syndrome when compared to Pfeiffer syndrome, is accounted for by the high proportion of younger cases of Apert syndrome undergoing radiographic examination in relation to an older Pfeiffer population.

The morphological anomalies which affected all three syndromes included hypoplasia or enlargement of the humeral epicondyles; the radial head exhibited "mushrooming" in both Pfeiffer and Apert syndromes, while a "square" ulnar shaft was seen in Apert syndrome. The joints were a common site for anomalies in all three syndromes, with radial head subluxation or dislocation in 5/22 cases of Crouzon syndrome, 8/16 cases of Pfeiffer syndrome and 16/36 cases of Apert syndrome. Anomalies of the epiphyses were also seen in all three syndromes with delay occurring in 4/22 cases of

Crouzon syndrome, 2/16 cases of Pfeiffer syndrome (with 11/16 cases demonstrating an absent epiphyses), and 11/36 cases of Apert syndrome demonstrating epiphyseal delay.

Fusions were seen to occur in examples of all three syndromes. In Crouzon syndrome there was a single case with all the articulations affected. There was a similar single case of complete joint synostosis in Pfeiffer syndrome, but in addition there were 3/16 cases with humero-ulnar synostosis, and 2/16 cases with radio-ulnar synostosis. In Apert syndrome there were 4/36 cases with humero-ulnar synostosis and a single case with humero-radial synostosis.

Previous reports have found radiological anomalies of the elbows in Crouzon syndrome only occasionally, which contrasts to this investigation where they occured in a over a third of all cases (Chapter Two). Similarly, in Pfeiffer syndrome elbow anomalies have been reported as occurring rarely (Cohen, 1986; Gorlin *et al.,* 1990), but in this study radiological anomalies were identified in 11/16 cases suggesting that elbow anomalies are common. The radiological anomalies in Apert syndrome were less than a previous report (Cohen and Kreiborg, 1993c), but this can be accounted for by the difference in ages of the populations in each study.

Comparison of the pattern of anomalies for each syndrome produces similar findings to the patterns in the hands and the feet suggesting an increasing range of severity for the three syndromes resulting from mutations of the FGFR 2 gene. This extends in broad terms from the mildly affected Crouzon syndrome, to the more severely affected Pfeiffer and Apert syndromes, although individual cases could have severe anomalies. The absence of anomalies in

Saethre-Chotzen syndrome again suggests that a different mechanism is responsible for the production of the anomalies in Saethre-Chotzen syndrome.

In conclusion the elbows have been shown to be a site which commonly exhibits anomalies in Crouzon, Pfeiffer and Apert syndromes, but not Saethre-Chotzen syndrome.

THE SHOULDERS

The shoulders demonstrated anomalies in Crouzon, Pfeiffer and Apert syndromes but not in Saethre-Chotzen syndrome. The anomalies recorded are compared in Table 6.5.

It is interesting to note that unlike other joints studied, there were no cases of fusions seen in any cases of any syndrome.

In comparison with previous reports there is just a single report of fusion of the shoulders in an adult with Crouzon syndrome (Proudman *et al.*, 1994), but no reports of this occurring in either Pfeiffer or Saethre-Chotzen syndromes. However, there have been three reported cases of gleno-humeral ankylosis in Apert syndrome (Yohenobu *et al.*, 1982; Kasser and Upton, 1991; Cohen and Kreiborg, 1993c). The findings of this study, and the few previous reports, suggests that fusion of the shoulder is exceptional.

The finding of an enlarged acromium and hypoplastic glenoid (usually symmetrically) were common to both Pfeiffer and Apert syndromes. The epiphysis of the upper humeral head also commonly displayed radiographic anomalies with delay in 8/30 cases of Apert

TABLE 6.5 COMPARISON OF THE SHOULDER ANOMALIES

	Common (>50% cases)	Uncommon (<50% cases)
Crouzon	None.	Epiphyseal delay.
Pfeiffer	Enlarged acromium.	Hypoplastic glenoid, Delay in upper humeral epiphysis, Humeral head flattened.
Apert	Enlarged acromium, Hypoplastic glenoid.	Delay in upper humeral epiphysis, Varus deformity of humeral head, Humeral head flattened.
Saethre-Chotzen	None.	None.

syndrome, 4/16 cases of Pfeiffer syndrome and a single case 1/13 case of Crouzon syndrome.

Comparison of the pattern of anomalies for each syndrome again produces similar findings to the patterns present in the hands, feet and elbows. An increasing range of severity for the three syndromes, extending in broad terms from the mildly affected Crouzon syndrome, to the more severely affected Pfeiffer and Apert syndromes was seen. The absence of anomalies in Saethre-Chotzen syndrome cases again suggests that a different mechanism is responsible for the production of the anomalies in that syndrome.

OTHER SITES

THE KNEES

The knees were clinically unremarkable and few cases underwent radiographic examination. The radiographs were normal in the four cases of Apert syndrome and in two cases of Saethre-Chotzen syndrome examined. However, this contrasts to the findings in Pfeiffer syndrome in which the upper tibial epiphysis was abnormal in all seven cases undergoing radiographic examination. In addition the bone age was abnormal in relation to the chronolgical age when compared to standards (Pyle and Hoerr, 1969). In Crouzon syndrome a single case had minor anomalies of absent tibial spines and a flared metaphysis.

These findings of the absence of anomalies of the knee in Apert syndrome are different to the results for the hands, feet, elbows and

shoulders in the same syndrome. However, review of the literature shows just a single case of joint synostosis at the knee (Cohen and Kreiborg, 1993c), which also suggests the knee is rarely affected. This is curious, because even in the most severely affected Apert syndrome cases, the knee appears to be normal. This contrasts to the results of radiographic examinations of the knee in Pfeiffer syndrome, which were all anomalous. The underlying mechanism in which the knee is unaffected in Apert syndrome is unclear, but warrants further investigation.

There may be a clinical application of these results using the method of bone ageing of infants and the radiographs of the knees (Pyle and Hoerr, 1969). The diagnosis on clinical grounds of atypical Pfeiffer and Crouzon cases can be difficult (Anderson *et al.*, 1996a). However, the five infant cases of Pfeiffer syndrome all had marked delay in bone age when compared to standards, while those with Crouzon syndrome were age appropriate. Radiological investigation and assessment of bone age of the knee may assist in the differential diagnosis.

THE PELVIS

The pelvis in all six cases of Apert syndrome demonstrated anomalies, which included enlargement of the greater trochanters, a shortened femoral neck and hypoplastic acetabula. No pelvic radiographic examinations had been undertaken in patients with Pfeiffer syndrome despite a case report of anomalies at this site (Saldino *et al.*, 1972). One of two cases of Crouzon syndrome

examined had hypoplastic acetabula. The numbers of cases undergoing investigation of the pelvis were very small which precludes any patterns of anomalies from becoming evident. The pelvis in Saethre-Chotzen syndrome was normal in the two cases which underwent radiological investigation, and this contrasts with a single report of an anomalous pelvis (Freidman *et al.*, 1977).

Overall, further investigation will be required to determine whether there is a discernable pattern of pelvic anomalies, although there is some evidence from this study, for Apert syndrome, to suggest that such a pattern may exist.

THE WRISTS

No formal wrist views were available for either Crouzon or Apert syndrome cases. Wrist views were obtained in five cases of Pfeiffer syndrome. The only morpholgical anomaly seen was of widening of the distal radius in two cases. However, in two further cases, a dislocation of the humero-ulnar joint at the elbow produced a secondary deformity of shortening of the ulnar at the wrist. This suggests that anomalies of morphology (not clinically evident) can occur, but the presence of elbow anomaly (which has been shown to regularly occur in Crouzon, Pfeiffer and Apert syndromes) may result in secondary deformity at the wrist. It is interesting that there are no previous reports of anomalies at this site, even in Apert syndrome, suggesting that this site (like the knee), is a spared site.

Curiously, the wrists were noted to be anomalous in hand radiographs of 4/22 cases of Saethre-Chotzen syndrome,

demonstrating mild flattening of the radial head. This again suggests that the mechanism producing the anomalies in this condition is different to that in the other three syndromes.

THE ANKLES

The radiographs of the ankles of two cases of Apert syndrome showed anomalies of both morphology and fusion, but two cases with Crouzon syndrome were normal. No views of the ankles were available for Pfeiffer syndrome cases. No previous reports of anomalies of the ankles could be found for any of the four syndromes.

This finding of both morphological changes and fusion contrasts with the absence of anomalies in the knees in Apert syndrome, but is similar to the findings in the feet. Further studies would reveal the significance of these findings. One of the two cases of Saethre-Chotzen syndrome undergoing radiographic examination of the ankles demonstrated tallipes equinovarus but no other anomalies, which suggests that the anomalies of the ankles may not be a feature of this syndrome.

THE CHEST WALL

There were no anomalies of the ribs seen in any of the syndromes. Only a single report of rib anomalies, a hypoplastic twelfth rib, could be found in Pfeiffer syndrome (Saldino *et al.,* 1972). It could be that

these occasional rib anomalies are the result of the congenital malformations of the lower spine because deformity of the ribs has been reported as occurring secondarily to the formation of "Butterfly" vertebae in the normal population (Muller *et al.*, 1986).

Pectus excavatum has been reported as not being uncommon in Apert syndrome (Cohen and Kreiborg, 1993c). The absence of this finding in this study contrasts with the previous report, and contributes to the doubt over the association of chest wall anomalies with any of the four syndromes.

VISCERAL ANOMALIES

Few visceral anomalies were detected in any of the children with one the four craniosynostosis syndromes studied. Visceral anomalies have been previously reported in Crouzon, Pfeiffer and Apert syndromes (Proudman *et al.,* 1994; Cohen, 1993a; Cohen and Kreiborg, 1993a). Development of the hands and feet occurs around the fifth week of intrauterine life (Fitzgerald and Fitzgerald, 1994). At the same period of time the other developmental processes occurring include the development and closure of septium primum in the heart; the mesonephric ducts reach the cloaca, and the metanephric buds appear. If anomalies at the visceral sites are part of these syndromes, then abnormal FGFR's should be present, and might be expressed at these sites at the same period of intrauterine development.

FGFR 2 receptors have been observed in the kidney, but not in the heart of adults (Johnson and Williams, 1993). Urogenital anomalies

in all of these syndromes were rare, with single cases of hypospadias in Crouzon and Saethre-Chotzen syndromes, but no genitourinary anomalies in either Pfeiffer or Apert syndrome. The low incidence of visceral anomalies may be due to apparent failure of expression of an abnormal FGFR 2. This could be due either to the absence of receptors at these sites at this time, or by the expression of a different isoform of abnormal FGFR 2 to that expressed in the hands and feet, which could have different biological behaviour. The expression of different isoforms in early embryogenesis is well established (Orr-Urtreger *et al.,* 1993).

Curiously, the association between Saethre-Chotzen syndrome, which is not the result of FGFR 2 gene mutation, and both genitourinary and cardiac anomalies has been recognised (Bartosocas *et al.*, 1970; Aase and Smith 1970). The small number of anomalies in this present study contrasts with the previously published report which found that urogenital and cardiac anomalies occur in 10% of Apert syndrome cases, and even this figure may underestimate the incidence (Cohen and Kreiborg, 1993a). Although this difference is difficult to explain it may be due to the selection of the different populations, as the previous report of Cohen and Kreiborg (1993a), includes the visceral anomalies found at twelve post-mortem examinations.

Cardiac anomalies are not uncommon in the general population, Crouzon, Pfeiffer and Apert patients all on occasion demonstrated cardiovascular anomalies in this series. Interestingly, there is an association between cardiac defects in nonsyndromic sagittal synostosis where 4% of cases are affected (Hunter and Rudd,

1976), and between mitral valve prolapse in skeletal deformities of the maxillofacial region where 23% of cases have been reported (Waite and McCallum, 1986). Thus, there is little evidence to suggest that an association of cardiac anomalies with the four syndromes studied, is other than by chance.

In conclusion, there is little evidence for concurrent production of anomalies of the viscera, due to abnormal FGFR expression at the same embryological period that hand and feet anomalies are produced.

GENETICS

The investigation of correlations between the phenotype and genotypes for Crouzon, Pfeiffer and Apert syndromes has yielded inconclusive results. In Crouzon syndrome, and to a lesser extent Pfeiffer syndrome, the number of different genotypes has resulted in only a few cases of the corresponding phenotype. However, the preliminary results suggest that there may indeed be some correlation between the site and severity of anomalies and a particular genotype. Clearly, this will be resolved as the number of identified genotypes in both of these syndromes increases. In Apert syndrome almost all cases belong to one of two genotypes, so comparison of the anomalies at different sites in relatively larger populations is possible. This has previously been attempted using mainly craniofacial and visceral features, (Park *et al.,* 1995b; Wilkie *et al.,* 1995b; Slaney *et al.,* 1996). Significant differences have been claimed with cleft palate more common in those with the Ser252Trp

mutation, while the degree of syndactyly of the hands and feet was more severe in the Pro253Arg group (Wilkie *et al.,* 1995b; Slaney *et al.,* 1996). However, these results contradict the findings of an earlier study (Park *et al.,* 1995b), so this controversy remains unresolved. The results of the present study, investigating the differences of the skeletal manifestations was limited by the small numbers in each group and mismatching of age. Further studies are required to show whether there are phenotypic differences related to genotype and some of the skeletal anomalies highlighted in this study could be used to investigate this.

The mechanism by which a mutation in Crouzon, Pfeiffer and Apert syndrome produces a particular phenotype involves dysfunction of the FGFR. This could be most easily explained by the changes in the three dimensional structure of the receptor altering ligand (FGF) binding, and hence altering function. This change in the receptor structure and the possible effect on function is supported by the many cases of Crouzon and Pfeiffer syndromes who have mutations affecting the cysteine residue in the third immunoglobulin domain of FGFR 2. This site is known to be important in ligand binding. Also, the different mutations may produce FGFR's with slightly different structures, depending on the amino acid substitution. Although these abnormal receptors may still bind the ligand in a normal manner, the subsequent FGFR initiated steps may be altered. This may help explain the phenotypic variation associated with different genotypes.

As far as Saethre-Chotzen is concerned, although the mutations responsible have not yet been identified, it would appear that the mechanism by which the cellular events are affected would appear to

differ from Crouzon, Pfeiffer and Apert syndromes, because FGFR'S are not affected. However, there are other craniosynostosis syndromes, for example Grieg syndrome and Adelaide craniosynostosis syndrome, who may have limb anomalies as part of their clinical features, and who have had the sites of their mutations identified to sites other than FGFR genes (Vortkamp *et al.,* 1993; Holloway *et al.,* 1995). This indicates that the production of limb anomalies is a complex processes and several different mechanisms can be involved.

GENERAL DISCUSSION AND CONCLUSIONS

This study has identified a wider range of anomalies, affecting more sites of the extracranial skeleton than have been currently described for Crouzon, Pfeiffer and Apert syndromes. These findings contrast with the distribution of the extracranial anomalies in Saethre-Chotzen syndrome which appear to be limited to the cervical spine, hands and feet. The finding of widespread anomalies affecting the extracranial skeleton in Crouzon, Pfeiffer and Apert syndromes is consistent with the expression and abnormal function of FGFR 2, which is known to be widely distributed, and important in osteogenesis (Reardon and Winter, 1995).

The finding of limb anomalies has previously been unrecognised in Crouzon syndrome, probably because they are only detecable radiologically. This finding is important because it casts doubt on the validity of the previously suggested hypothesis that differences in expression of limb anomalies is related to biological differences in the

mechanism of craniosynostosis found in Apert and Crouzon syndromes (Cohen, 1995).

The relationship of the extracranial anomalies to those affecting the cranial sutures are similar, in that, disease progression can affect the sites after birth. The number of FGFR's in cranial sutures, affected by craniosynostosis in Crouzon syndrome, is lower compared with unaffected cranial sutures in Crouzon syndrome, and also compared to the cranial sutures of unaffected individuals (Bresnick and Schendel, 1995). It has been proposed by Wilkie et al (1995a) that activation of FGF's or FGFR's could be a possible mechanism by which the mutations which result in craniosynostosis produce their effects at a molecular level.

The relationship between the severity of the craniosynostosis and the extent and severity of extracranial anomalies would appear to be inconsistent. This was unexpected, but was best demonstrated in Pfeiffer syndrome where a patient with a cloverleaf cranial deformity had both a normal cervical spine and elbows (case 21, Chapter Three). This finding was different to the results of an earlier, but smaller study, which found that all Pfeiffer syndrome cases with cloverleaf deformity had cervical fusions (Moore *et al.,* 1995).

The progressive nature of the fusions during childhood which have been observed in all four syndromes is curious. Progressive fusions of the hands, feet and elbows in Crouzon, Pfeiffer and Apert syndromes could be due to the abnormal FGFR's. However, the anomalies of the cervical spine may involve other mechanisms because progressive fusion can also occur in Saethre-Chotzen syndrome. The mechanism of progressive fusion, and its relation to

FGFR expression is currently unclear. It has been proposed, from the results of experiments in mice, that the progressive fusions of the hands in Apert syndrome could be due to deficiencies of the embryonic mesenchyme surrounding the skeletal elements (*Wilkie et al.,* 1995a). This normally develops into connective tissue which envelops each of the different skeletal elements (Wilkie *et al.,* 1995a), and may normally be of importance in preventing fusions of skeletal elements. A similar mechanism may account for the progressive fusions of the hands in Crouzon and Pfeiffer syndromes. Similarly, abnormal mesenchyme may also be important in the production of progressive fusions at other sites of the extracranial skeleton in Crouzon, Pfeiffer and Apert syndromes. The fusions of the spine may occur as the result of a different process because they are also seen in Saethre-Chotzen syndrome. Also the embryological development of the cervical spine differs from limb development, in that it is derived from cervical somites (O'Rahilly and Benson, 1985). However, a common final mechanism which produced a generalised abnormality of connective tissue, could also account for the anomalies at many other sites. There is some evidence to support the possibility of a generalised connective tissue disorder in Apert syndrome, where it has been reported that there are abnormalities of chondroitin sulphate metabolism (Kaye *et al.,* 1973) and abnormal accumulations of palatal mucopolysaccharides (Soloman *et al.,* 1973). The FGFR gene is widely expressed in the cervical somites and in the devloping limb in mesenchyme from which connective tissues are derived. The FGFR gene is also expressed later in the vertebral column (Thompson *et al.,* 1996). It has been suggested

that the different mutant FGFR genes may alter the temporal and spatial patterns of FGFR expression, which may be particularly important in the cervical spine. Such a mechanism could explain the differences in the levels of cevical spine fusions in Crouzon, Pfeiffer and Apert syndromes, as it has been established that more caudal levels develop later (O'Rahilly and Benson, 1985).

The wider range of extracranial anomalies associated with Apert, Crouzon, Pfeiffer or Saethre-Chotzen syndromes are often subtle, and can only detected radiologically, yet these have consequences both for the clinical management, and also wider scientific implications for understanding normal and abnormal human development.

There are several consequences which follow as a result of this research.

1) Firstly, the new knowledge of the extent of the range of extracranial anomalies associated with each syndrome will assist those attempting to make a diagnosis on clinical features alone, without the assistance of D.N.A. analysis. This applies particularly to patients where the craniofacial features are similar (especially Pfeiffer and Crouzon syndromes) and in atypical phenotypes. An example could include a phenotype where following the clinical examination the differential diagnosis includes: Non-syndromic bicoronal synostosis, Saethre-Chotzen syndrome, or Pfeiffer syndrome. In such a case, radiological appearances of the hands, which have characteristic anomalies (see Chapters Three and Five), may assist diagnosis. Similarly, the diagnosis of infant phenotypes where the differential diagnosis includes Pfeiffer and Crouzon syndrome may be

assisted by radiographs of the knees, and by bone ageing (see Chapters Two and Three).

However, there are some features which are now less significant. For example, broad big toes have been described as classically found in Pfeiffer syndrome (Gorlin *et al.,* 1990). This study confirms that broad phalanges of the big toes can also be found radiologically in cases of Crouzon and Saethre-Chotzen syndromes. Consequently, this finding, on its own, requires cautious interpretation if attempting to make a clinical diagnosis.

Secondly, the knowledge of the wider range of anomalies, associated with these syndromes, will alert clinicians involved in the care of individuals with these syndromes to potential problems at sites other than the craniofacial region, that may arise during the child's development. The confirmation that the fusion process is often progressive in the cervical spine, hands, feet and elbows may result in secondary deformity, with clinical sequelae in later childhood and adulthood. Corrective surgery has often not been undertaken until the deformities are severe, and disability evident. The exception to this is the hands where surgical intervention in Apert syndrome has been performed in some Centres to release syndactylies. The timing of this surgery varies at different United Kingdom Centres, starting at between six months and four years of age. All the patients studied at Great Ormond Street Hospital underwent early corrective hand surgery in infancy, to improve function. Surgical intervention to release syndactylies in the hands may have prevented transverse phalangeal fusions developing. It was noted that in some of the unoperated feet of the same patients, transverse phalangeal

fusions developed during childhood, increasing the level of local deformity. This raises the possibility that if early surgery had not been performed on the hands, similar fusions may have developed. These findings support the recommendation that early corrective surgery should be performed (Barot and Caplan, 1986), not just on the hands but perhaps also on the feet (first web space). Treatment of the anomalies of other joints of the limbs may benefit from co-operation with the specialties of Rheumatology and Orthopaedic surgery, as increasing numbers of individuals survive into adulthood.

(4) Thirdly, the knowledge gained from the radiological examinations of comparatively large numbers of cases, has led to the development of protocols for radiological examination of subsequent patients with these syndromes. The protocol developed is summarised in Table 6.6. These protocols include early assesment of the cervical spine for all of the syndromes: monitoring existing fusions or the presence of "Butterfly" vertebrae or hypoplastic C1, can be used by the clinician as a guide to later progressive fusion. Radiographs of the cervical spine require repetition throughout childhood, particulaly prior to general anaethesia (where neck extension is likely), as the fusion process has been shown in all of these complex craniosynostosis syndromes to be progressive.

Finally, the clear demonstration that mutations affecting the same cell receptor, (and in the case of Crouzon and Pfeiffer syndrome the same genotypes) can have profoundly different phenotypic expression, highlights the complexity of the biological processes involved in human development. The patterns and incidence of congenital anomalies and fusion patterns were variable for all four

syndromes. The results of this study broadens the overlap of clinical features associated with Crouzon and Pfeiffer syndromes. This is best shown by case 5 Chapter Two and case 20 Chapter Three which both have a Cys342Ser FGFR 2 substitution. This raises the possibility that instead of being clinically distinct syndromes, Pfeiffer and Crouzon syndromes are instead part of a spectrum of related disorders, (which could also include Jackson-Weiss syndrome). There is indirect genetic evidence to support this concept with the discovery of an increasing number of mutations which can produce either phenotype, and more recently the first reports of families exhibiting intrafamilial variability. The first example consisting of a Pfeiffer phenotype, and two members with craniosynostosis but no limb anomalies (Meyers *et al.,* 1996), and the second, a report of a mother with a Crouzon phenotype, who produced a Pfeiffer phenotype child (Holloway *et al.,* 1997). In the case of the latter, the mutation was C1205G, and affected the Cysteine342 codon. Previously, this mutation had only been identified in Crouzon syndrome.

It has been suggested that the craniosynostosis syndromes resulting from FGFR 2 mutations form part of a continuous spectrum of related craniosynostotic and digital disorders (Meyers *et al.,* 1996). The results of the present study neither prove nor entirely refute this suggestion. Support for the concept of a spectrum of anomalies associated with FGFR mutations, is best demonstrated in Crouzon, Pfeiffer and Apert syndromes, by the common anomalies in the hands of carpal fusions; in the feet by common anomalies of phalangeal and tarsal fusions and in the elbows by radial head

dislocation and epiphyseal delay. There is also support from the results of the identification of the anomalies present in a patient who had one of the genotypes common to both Pfeiffer and Crouzon syndromes (case 5 Chapter Two). This patient exhibited a mixed picture of anomalies of varying severity at different extracranial sites. However, when the differences in the pattern of cervical spine anomalies, and the appearances of the knee radiographs in early childhood are considered, the results of this study could still support the concept of different syndromes, with a distinct range of anomalies for Crouzon and Pfeiffer syndromes. The question will be resolved by the identification of more genotypes for patients who have undergone careful investigation to establish their phenotypic findings.

The relationship between the genetic mutation and the molecular mechanisms which result in the extracranial anomalies requires elucidation but the FGF/FGFR signalling pathway is important. The evidence from the study of Saethre-Chotzen syndrome cases suggests that other mechanisms are also involved. Regulatory genes, including MSX2 play a role in embryological development (Johnston and Bronsky, 1995), and a mutation of this gene is the cause of yet another craniosynostosis syndrome (Jabs *et al.,* 1993)

The findings of this study which demonstrate a wider range of extracranial anomalies exhibited by individuals with Crouzon, Pfeiffer, Apert and Saethre-Chotzen syndromes, than previously reported, may aid the Developmental Biologists and Molecular Biologists as they attempt to understand normal and abnormal human development.

Table 6.6 PROTOCOL FOR RADIOGRAPHIC EXAMINATIONS

	3 - 6 Months	2 - 4 Years	8 - 12 Years
Crouzon			
	Cervical spine	Cervical spine	Cervical spine
			Hands
			Feet
			Elbows
Pfeiffer			
	Cervical spine	Cervical spine	Cervical spine
	Skeletal survey		Hands
			Feet
			Elbows
			Shoulders
Apert			
	Cervical spine	Cervical spine	Cervical spine
	Skeletal survey	Feet	Hands
			Feet
			Elbows
			Shoulders
			Pelvis
			Knees
Saethre-Chotzen			
	Cervical spine	Cervical spine	Cervical spine
	Hands		Hands
			Feet

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APPENDIX ONE - PUBLICATIONS

Permission from my joint authors has been obtained for the inclusion of copies of all the papers published during the course of compiling this thesis. Permission from the publishers has also been obtained for those papers which are included in this thesis.

PAPERS

Anderson PJ, Hall CM, Evans RD, Hayward RD, Jones BM (1996).
The hands in Saethre-Chotzen syndrome.
Journal of Craniofacial Genetics and Developmental Biology. **16:** 228 - 233.

Anderson PJ, Hall CM, Evans RD, Hayward RD, Jones BM (1996).
Cervical spine in Pfeiffer syndrome.
Journal of Craniofacial Surgery. **7:** 275 - 279.

Anderson PJ, Hall R, Smith PJ (1996).
Finger duplication in Apert's syndrome.
Journal of Hand Surgery. **21B:** 649 - 651.

Anderson PJ, Smith PJ, Jones BM, Hayward RD (1996).
Additional metatarsal bones in Apert syndrome.
The Foot. **6:** 37 - 38.

Anderson PJ, Smith PJ, Evans RD, Jones BM (1996).
Asymmetrical anomalies of the feet in Apert syndrome.
The Foot. **6:** 195 - 196.

Anderson PJ, Hall CM, Evans RD, Jones BM, Hayward RD (1997).
Hand anomalies in Crouzon syndrome.
Skeletal Radiology. **26:** 113 - 115.

Anderson PJ, Hall CM, Evans RD, Hayward RD, Harkness WJ, Jones BM (1997).
The cervical spine in Crouzon syndrome.
Spine. **22:** 402 - 405.

Anderson PJ, Hall CM, Evans RD, Hayward RD, Jones BM (1997).
The cervical spine in Saethre-Chotzen syndrome.
Cleft Palate-Craniofacial Journal. **34:** 79 - 82.

Anderson PJ, Hall CM, Smith PJ, Evans RD, Hayward RD, Jones BM.
The hands in Pfeiffer syndrome.
Journal of Hand Surgery. *In press*.

Anderson PJ, Hall CM, Evans RD, Hayward RD, Jones BM.
The feet in Crouzon syndrome.
Journal of Craniofacial Genetics and Developmental Biology.
In press.

Anderson PJ, Hall CM, Evans RD, Hayward RD, Jones BM.
The feet in Pfeiffer syndrome.
Journal of Craniofacial Surgery.
In press

Anderson PJ, Hall CM, Evans RD, Hayward RD, Jones BM.
Knee radiographs in Pfeiffer and Crouzon syndrome.
Plastic and Reconstructive Surgery. *In press*

ABSTRACTS

Anderson PJ, Hall CM, Evans RD, Hayward RD, Jones BM.
Cervical spine anomalies in syndromic craniosynostosis.
European Journal of Orthodontics. 1996; **18**: 402 - 403.

Anderson PJ, Hall CM, Evans RD, Hayward RD, Jones BM.
Limb anomalies in craniosynostosis syndromes.
Clinical Science. *In press.*

COMMUNICATIONS

Anderson PJ, Hall CM, Evans RD, Hayward RD, Jones BM.
Cervical spine anomalies in syndromic craniosynostosis.
72nd Congress European Orthodontic Society, July 1996.

Anderson PJ, Hall CM, Evans RD, Hayward RD, Jones BM.
Cervical spine anomalies in syndromes with craniosynostosis.
British Cervical Spine Society Annual conference, November 1996.

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Cervical spine anomalies in syndromes with craniosynostosis.
British Craniofacial Society Scientific Meeting, April 1997.

Anderson PJ, Hall CM, Evans RD, Hayward RD, Jones BM.
Limb anomalies in craniosynostosis syndromes.
Medical Research Society Annual Scientific meeting, May 1997.